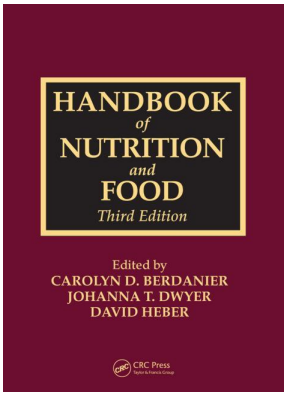

Handbook of Nutrition and Food

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Microbiological Safety of Foods

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INTRODUCTION

The microbiological safety of foods is a major concern to consumers and to the food industry. Despite considerable progress made in technology, consumer education, and regulations, food safety continues to be a major challenge to our public health and economy. During the last decade, food safety received considerable attention due to the emergence of several new foodborne pathogens and the involvement of foods that traditionally have been considered safe, in many foodborne disease outbreaks. Further, industrialization of the food supply through mass production, distribution, increased globalization, and consumer demands for preservative-free, convenience foods and ready-to-eat meals highlights the significance of the microbial safety of foods. Recently, the U.S. Centers for Disease Control and Prevention (CDC) reported an estimated 48 million cases of foodborne illnesses, with 130,000 hospitalizations and 3000 deaths in the United States annually.[1] Besides the public health impact, outbreaks of foodborne illness impose major economic losses to both the food industry and society. The annual estimated cost of foodborne illnesses accounts for approximately $152 billion with nearly $32 billion attributed to contaminated produce.[2,3] Moreover, isolation of antibiotic-resistant foodborne bacteria as etiologic agents implicated in outbreaks has been increasingly reported. According to the Center for Science in the Public Interest (CSPI), 35 foodborne outbreaks during the last three decades were caused by bacteria resistant to at least one antibiotic.[4] The various microbiological hazards associated with foods can be classified broadly as bacterial, viral, fungal, and parasitic.

Bacterial Foodborne Pathogens

Bacteria are major agents causing microbial foodborne illnesses and account for an estimated 4.8 million foodborne illnesses annually in the United States (Table 3.1).[5] Bacterial foodborne diseases can be classified into foodborne infections and foodborne intoxications. Foodborne infection is a condition caused by the ingestion of viable cells of a pathogen. Foodborne intoxication is a condition in which preformed toxins in the food produced by a toxigenic pathogen act as the underlying cause of disease.[6] The various bacterial pathogens associated with foodborne diseases are discussed in the following.

Shiga Toxin Escherichia coli (STEC)

There are six different pathotypes of *E. coli*, including enteropathogenic *E. coli* (EPEC), enterotoxigenic *E. coli* (ETEC), enteroinvasive *E. coli* (EIEC), diffusely adhering *E. coli* (DAEC), enteroaggregative *E. coli* (EAEC), and enterohemorrhagic *E. coli* (EHEC),[7] that have been associated with gastrointestinal illness. Among these, EHEC, which produce Shiga toxins (verotoxins), are most frequently implicated in foodborne disease outbreaks and generally classified into O157 and non-O157 serogroups. EHEC O157:H7 emerged in 1982 as a foodborne pathogen and is now recognized as a major public health concern in the United States.[8] A recent report indicated that *E. coli* O157:H7 causes an estimated 63,000 cases annually in the United States with 2,138 hospitalizations and 20 deaths, accounting for a loss of $607 million.[3] Although approximately 50% of the reported outbreaks in the United States have been associated with consumption of undercooked beef burgers, a wide variety of other foods, including raw milk, roast beef, venison jerky, salami, yogurt, lettuce, unpasteurized apple juice, cantaloupe, alfalfa sprouts, and coleslaw, have been implicated as vehicles of *E. coli* O157:H7 infection.[9,10] Fresh fruits and vegetables are increasingly being identified as vehicles of EHEC infections around the world.[7,11] In the United States, iceberg lettuce and spinach have been implicated in several outbreaks.[7] In addition, outbreaks involving person-to-person and waterborne transmission have been reported.[9] Cattle have been implicated as one of the principal reservoirs of *E. coli* O157:H7.[12–15] In adult cattle, *E. coli* O157:H7 primarily colonizes the terminal rectum, particularly an anatomical area within the terminal rectum referred to as the rectoanal junction.[16] *E. coli* O157:H7 can survive in bovine feces for many months,[17] hence potentially contaminating cattle, food, water, and the environment. Although surveys conducted in the late eighties and nineties estimated a low fecal prevalence of *E. coli* O157:H7 in cattle,[15,18,19] later studies using improved enrichment and isolation procedures have showed that the overall prevalence of *E. coli* O157:H7 in cattle may be significantly higher than originally estimated.[20–23] A survey conducted by Elder et al.[20] indicated that of the 29 feedlots of cattle presented for slaughter in the Midwestern United States, 72% had at least one *E. coli* O157-positive fecal sample and 38% had positive hide samples. The study revealed an overall *E. coli* O157 prevalence of 28% (91 out of 327) in feces and 11% (38 out of 355) in hide. Subsequent research by others estimated that up to 30% of cattle are asymptomatic carriers of EHEC.[24,25] Recently, Woerner et al.[26] observed a relationship between fecal incidence rate (FIR) in cattle and hide contamination by EHEC. When FIR is more than 20%, hides positive for EHEC were about 26%, whereas when FIR was lower than 20%, only 5% of the cattle hides were contaminated. Studies by other researchers revealed that the prevalence of *E. coli* O157 in feedlots in the United States can reach 63%, particularly during the summer, under muddy conditions, or with feeding of barley.[27,28] However, other investigations revealed that EHEC shedding could be as high as 80% during the summer to as low as 5%–10% during winter,[29,30] a factor that could be attributed to the greater occurrence of foodborne outbreaks caused by EHEC during the summer.[31] These results are of particular concern because high fecal shedding and the presence of *E. coli* O157:H7 on hides would lead to contamination of foods of bovine origin with the pathogen during slaughtering and processing operations.[32] In addition, many *E. coli* O157:H7 outbreaks involving nonbovine foods, such as fruits and vegetables, are linked to cross contamination of the implicated food with contaminated bovine manure.[33–36] Direct zoonotic and environmental transmission is a newly recognized mode of *E. coli* O157:H7 spread to humans. Contact with farming

TABLE 3.1
Bacterial Foodborne Pathogens

Microorganism	Biochemical and Growth Characteristics	Sources/Reservoirs	Examples of Vehicles	Estimated No. of Foodborne Cases Annually in the United States[2,3]	Incubation Period, Symptoms, and Duration	Detection Methods	Control/Prevention
E. coli O157:H7	Gram negative, facultative anaerobe, nonspore-forming, optimum growth at 37°C–40°C, inability to grow at ≥44.5°C in the presence of selective agents, inability to ferment sorbitol within 24 h, does not produce glucuronidase, acid tolerance	Cattle, humans	Raw or undercooked beef, unpasteurized milk and apple juice, lettuce, alfalfa sprouts, water	63,153	3–9 days Severe abdominal cramps, watery diarrhea that can become bloody, absence of fever, kidney failure, seizures, coma Duration is days to weeks	Cultural methods followed by confirmatory biochemical tests[374,375] Latex agglutination assay[376,377] ELISA[378–380] PCR[381–384] Immunomagnetic separation[384] biosensors[385,386] Fourier transform infrared (FT-IR) Spectroscopy and chemometrics[387] Bacteriophage-based assay[388] DNA microarray[389]	Adequate cooking of beef, pasteurization of milk and apple juice, use of potable water for drinking, avoid eating raw alfalfa and vegetable sprouts, good personal hygiene
Salmonella spp. (nontyphoid)	Gram negative, facultative anaerobe, oxidase negative, catalase positive, nonspore-forming, growth at 5°C–47°C, optimum growth at 37°C, metabolize nutrients by respiratory and fermentative pathways	Cattle, swine, poultry, humans	Raw or undercooked meat, poultry, eggs, and milk, untreated water	1,027,561	6–72 h up to 4 days Abdominal cramps, diarrhea, fever, chills, headache, and vomiting Duration is few days to 1 week, occasionally up to 3 weeks	Cultural methods followed by confirmatory biochemical tests[390–392] Latex agglutination assay[393] ELISA[394] Immunoassay[395] PCR[396–399]	Adequate cooking of food, avoid cross contamination of raw foods of animal origin with cooked or ready-to-eat foods, avoid eating raw or undercooked foods of animal origin, use of potable water, good personal hygiene
Salmonella typhi	Gram negative, facultative anaerobe, ferment D-xylose	Humans	Raw milk, shellfish, raw salads, undercooked foods	1,821	7–28 days Remittent fever with stepwise increments over a period of days, high temperature of 103°F–104°F, abdominal pain, diarrhea, and headache Duration is up to 3 weeks	Biochemical tests[400] Latex test[401] ELISA[402] PCR[403–405] Quantum dot assay[406] ELISA[407]	Good personal hygiene and food handling practices, proper sewage systems, effective surveillance of known carriers

(*continued*)

TABLE 3.1 (continued)
Bacterial Foodborne Pathogens

Microorganism	Biochemical and Growth Characteristics	Sources/Reservoirs	Examples of Vehicles	Estimated No. of Foodborne Cases Annually in the United States[2,3]	Incubation Period, Symptoms, and Duration	Detection Methods	Control/Prevention
Campylobacter jejuni and *C. coli*	Gram negative, microaerophilic, nonspore-forming, optimal growth at 42°C, CO_2 is required for good growth, growth optimal in 3%–6% O_2, sensitive to dehydration, survives best at refrigeration temperature	Poultry Swine Cattle Sheep Wild birds	Raw or undercooked chicken, pork, and beef and unpasteurized milk	845,024	1–11 days, usually 2–5 days Abdominal pain, diarrhea, malaise, headache, fever Duration is up to 10 days	Cultural methods followed by confirmatory biochemical tests[408,409] Immunoassay[410,411] PCR[412–418] Quantum dot sandwich assay[419] Loop-mediated isothermal amplification (LAMP) assay[420] Biosensor[421] DNA microarray[422]	Adequate cooking of meat; avoid cross contamination of raw foods of animal origin with cooked or ready-to-eat foods; pasteurization of milk
Shigella spp.	Gram negative, facultative anaerobe, nonspore-forming, does not ferment lactose, growth at 10°C–45°C, optimal growth at 37°C	Humans	Raw foods and water contaminated with human feces, prepared salads	131,254	1–7 days Severe abdominal and rectal pain, bloody diarrhea with mucus, fever, dehydration Duration is few days to few weeks	Cultural methods followed by confirmatory biochemical tests[423] ELISA[424,425] PCR[426–430] Apyrase-based colorimetric test[431] DNA microarray[432]	Good personal hygiene, adequate cooking of food, drinking potable water
Y. enterocolitica	Gram negative, facultative anaerobe, nonspore-forming, growth at 0°C–44°C, optimal growth at ca. 29°C, growth at pH 4.6–9.0, growth in presence of 5% NaCl but not 7% NaCl	Swine is principal reservoir of pathogenic strains. Humans can also act as a source through contaminated blood transfusion.	Undercooked or raw pork, especially tongue	97,656	1–11 days, usually 24–36 h Severe abdominal pain, nausea, diarrhea, fever, sometimes vomiting Duration is usually 2–3 days but may continue for up to 3 weeks	Cultural methods followed by confirmatory biochemical tests[433] PCR[434–436] Monoclonal antibody-based dot blot assay[437] LAMP assay[438] Mass spectrometry[439] DNA microarray[432]	Adequate cooking of pork, disinfection of drinking water, control of *Y. enterocolitica* in pigs, prevent cross contamination of pig viscera, feces, and hair with food and water

V. cholerae	Gram negative, facultative anaerobe, nonspore-forming, growth at 18°C–42°C with optimal growth at 37°C, growth is stimulated in the presence of 3% NaCl, pH range for growth is 6–11	Humans, marine waters, especially brackish water and estuaries	Undercooked or raw seafoods, vegetables fertilized with contaminated human feces or irrigated with contaminated water, water	84	1–3 days Profuse watery diarrhea, which can lead to severe dehydration, abdominal pain, vomiting Duration is up to 7 days	Cultural methods followed by confirmatory biochemical tests[440–442] ELISA[443,444] Immunoassay[445] PCR[446–451] Biosensor[450] LAMP assay[420,452] DNA microarray[432,453]	Safe disposal of human sewage, disinfection of drinking water, avoid eating raw seafood, adequate cooking of food
Vibrio parahaemolyticus	Gram negative, facultative anaerobe, nonspore-forming, growth in presence of 8% NaCl, optimal growth at 37°C with rapid generation time (ca. 10 min), growth at 10°C, sensitive to storage at refrigeration temperature	Coastal seawater, estuarine brackish waters above 15°C, marine fish, shellfish	Raw or undercooked fish and seafoods	34,664	9–25 h, up to 3 days, Profuse watery diarrhea, abdominal pain, vomiting, fever Duration is up to 8 days	Cultural methods followed by confirmatory biochemical tests[440,441] ELISA[454] PCR[455–460] LAMP assay[461] DNA microarray[432,462]	Adequate cooking of seafood, rapid chilling of seafoods, prevent cross contamination from raw seafoods to other foods and preparation surfaces
Vibrio vulnificus	Gram negative, nonspore-forming, optimal growth at 37°C	Coastal and estuarine waters	Raw seafood, especially raw oysters	96	12 h to 3 days Profuse diarrhea with blood in feces, fulminating septicemia, hypotension Duration is days to weeks	Cultural methods followed by confirmatory biochemical tests[440,441,463] ELISA[464,465] PCR[466–470] LAMP assay[469,471] DNA microarray[432,472]	Avoid eating raw seafood, especially raw oysters when have a history of liver disease or alcoholism
C. sakazakii	Gram negative, facultative anaerobe, nonspore-forming, α-glucosidase positive, phosphoamidase negative, growth at 5.5°C–37°C, tolerant to high osmotic pressure and desiccation	Not known	Dry, powdered infant formula	Not available	Sepsis, meningitis, meningoencephalitis, brain abscess, ventriculitis, hydrocephalus, necrotizing enterocolitis in infants Bacteremia, osteomyelitis, and pneumonia in elderly adults	Cultural and biochemical methods[473,474] PCR[475–478] DNA-microarray[477,479]	Proper refrigerated storage of reconstituted infant formula Avoid feeding nonrefrigerated formula and formula refrigerated for more than 24 h Prepared infant formula should not be kept warm in bottle heaters or thermoses

(*continued*)

TABLE 3.1 (continued)
Bacterial Foodborne Pathogens

Microorganism	Biochemical and Growth Characteristics	Sources/Reservoirs	Examples of Vehicles	Estimated No. of Foodborne Cases Annually in the United States[2,3]	Incubation Period, Symptoms, and Duration	Detection Methods	Control/Prevention
A. hydrophila	Gram negative, facultative anaerobe, nonspore-forming, oxidase positive, some strains are psychrotrophic (4°C) optimum growth at ca. 28°C	Aquatic environment, freshwater fish (especially salmonids)	Untreated water Undercooked seafoods, especially fish	Very few	24–48 h Abdominal pain, vomiting, watery stools, mild fever Duration is days to weeks	Cultural methods followed by confirmatory biochemical tests[480–483] ELISA[484] PCR[485–488] Biosensors[489] Indirect fluorescent antibody assay[490] Monoclonal antibody-based dot blot assay[491] LAMP assay[492] DNA microarray[493]	Avoid consumption of raw seafoods, avoid long-term storage of refrigerated foods, adequate cooking of foods, disinfection of drinking water
P. shigelloides	Gram negative, facultative anaerobe, nonspore-forming, oxidase positive, some strains are psychrotrophic	Fresh and estuarine waters, fish, and shellfish	Fish, shellfish, oysters, shrimp, and untreated water	Very few	1–2 days Abdominal pain, nausea, vomiting, diarrhea, chills, headache Duration is days to weeks	Cultural methods followed by confirmatory biochemical tests[480,481] PCR[494]	Avoid consumption of raw seafoods, disinfection of drinking water
L. monocytogenes	Gram positive, facultative anaerobe, nonspore-forming, growth at 2°C–45°C, optimal growth at 30°C–35°C, growth in presence of 10% NaCl	Soil, sewage, vegetation, water, and feces of humans and animals	Raw milk, soft cheese, pâte, ready-to-eat cooked meat products (poultry, hot dogs) and cooked seafoods (smoked fish), and raw vegetables	1,591	Few days to several weeks Flu-like symptoms such as fever, chills, headache Abdominal pain and diarrhea are present in some cases In pregnant women, spontaneous abortion and stillbirth Duration is days to weeks	Cultural methods followed by confirmatory biochemical tests[495–498] Immunoassay[499–501] PCR[502–507] Biosensors[508] LAMP assay[509] Fluorescent in situ hybridization (FISH)[510]	Proper sanitation of food processing equipment and environments; adequate cooking of meat and meat products; prevent recontamination of cooked products; proper reheating of cooked food; avoid drinking raw milk, avoid certain high-risk foods (e.g., soft cheeses and pâtes) by pregnant women and immunocompromised individuals

S. aureus (staphylococcal enterotoxin)	Gram positive, facultative anaerobe, nonspore-forming, coagulase positive, growth at 7°C–48°C, optimal growth at ca. 37°C, toxin production at a_w of 0.86; toxin is heat stable (can withstand boiling for 1 h)	Humans (nose, throat, and skin) and animals	Ham, chicken and egg salads, cream-filled pastries	241,148	2–6 h Abdominal cramps, nausea, vomiting, diarrhea, headache, chills, and dizziness Duration is up to 2 days	Cultural methods followed by confirmatory biochemical tests[511,512] PCR[513–517] Immunoassay[518–520] Detection of toxin by microslide gel double diffusion[521] FISH[522] ssDNA aptamer detection[523]	Good personal hygiene in food preparation and handling, adequate cooking of foods, proper refrigeration of cooked foods
C. botulinum (botulinum neurotoxin)	Gram positive, obligate anaerobe, spore-forming, produce seven potent neurotoxins A–G (only A, B, E, and rarely F associated with human illness); proteolytic strains grow at 10°C–50°C, and nonproteolytic strains can grow at 3.3°C; spores are resistant to normal cooking temperatures and survive freezing and drying	Soil, dust, vegetation, animals, birds, insects, and marine and fresh water sediments and the intestinal tracts of fish (type E)	Beef, pork, fish, vegetables, and honey (infant botulism)	55	12–36 h, can range from few hours to 8 days Very severe life-threatening intoxication, headache, fixed and dilated pupils, vertigo, blurred or double vision, lack of muscle coordination, dry mouth, difficulty in breathing Gastrointestinal symptoms include abdominal pain, nausea, vomiting, and constipation Duration is days to months (8 months)	Cultural methods followed by confirmatory biochemical tests[524] PCR[525–531] Detection of toxin by mouse bioassay[532] immunoaffinity chromatograpgy[533] mass spectrophotometry[534] immunodetection kit[535] LAMP assay[536] DNA microarray[537]	Boiling of foods will destroy toxin; adequate heat processing of home-canned foods; proper refrigeration of vacuum-packaged fresh or lightly cooked/smoked foods; acid-preserved foods should be below pH 4.6; discard swollen cans; avoid feeding honey to infants
C. perfringens	Gram positive, anaerobe, spore-forming, optimum growth at 37°C–47°C, grows slowly below 20°C	Soil, sewage, dust, vegetation, feces of humans and animals	Cooked meat and poultry, especially roast beef, turkey, and gravies	965,958	8–24 h Abdominal pain and diarrhea Duration is 1–2 days	Cultural methods followed by confirmatory biochemical tests[243] Latex agglutination test[538] Colony hybridization assay[539] ELISA[540,541] PCR[538,542–545] FISH[546] DNA microarray[547]	Adequate cooking of foods; cooked food should be rapidly cooled (<5°C) or held hot (>60°C); proper refrigeration and adequate reheating of stored cooked foods

(*continued*)

TABLE 3.1 (continued)
Bacterial Foodborne Pathogens

Microorganism	Biochemical and Growth Characteristics	Sources/Reservoirs	Examples of Vehicles	Estimated No. of Foodborne Cases Annually in the United States[2,3]	Incubation Period, Symptoms, and Duration	Detection Methods	Control/Prevention
C. difficile	Gram positive, spore-forming, anaerobic, showing optimal growth at human body temperature	Water, air, human and animal feces, soil	Ground beef, ground veal, veal chops, ground pork, chicken, vegetables	Not available	Abdominal pain, fever, fulminant colitis, toxic megacolon, sepsis, shock, mild diarrhea in asymptomatic carriers, relapse or reinfection within 2 months	Cultural methods followed by confirmatory biochemical tests[249] ELISA[548] PCR[549–551] LAMP assay[552] PCR ribotyping[553] DNA microarray[554]	Hospital setting: Limit use of antimicrobial drugs, wash hands between contact, use precautions for infected people with diarrhea, clean the environment meticulously Community setting: Proper cooking of meat[555]
B. cereus	Gram positive, facultative anaerobe, spore-forming; some strains can grow at 4°C–6°C, optimum growth at 28°C–37°C	Widely distributed in nature, soil, dust, vegetation	Cereals, fried rice, potatoes, cooked meat products, milk and dairy products, spices, dried foods	63,400	*Diarrheal syndrome* (toxic infection): 8–16 h Abdominal pain, watery diarrhea Duration is 24–36 h *Emetic syndrome* (preformed, heat-stable toxin): 1–5 h Nausea, vomiting, malaise, sometimes diarrhea Duration is 24–36 h.	Cultural methods followed by confirmatory biochemical tests[556] ELISA[557,558] Colony blot immunoassay[559,560] PCR[561–565] Tecra VIA kit[566] Oxoid BCET-RPLA kit[566] CHO cell culture assay[566] DNA microarray[567]	Adequate cooking of foods; cooked foods should be rapidly cooled (<5°C) or held hot (60°C); avoid leaving cooked foods at room temperature for long time
A. butzleri	Fastidious, gram negative, nonspore-forming, motile, spiral organisms, grows microaerobically and aerobically, ability to grow at 15°C differentiating it from *Campylobacter* Preferred temperature for growth is 30°C	Domestic and pet animals, birds including chickens and turkeys, humans	Increased isolation from raw meat products, surface and groundwater, foodborne transmission is not definitive	Unknown	Human enteritis characterized by persistent and watery diarrhea, vomiting, nausea, and fever	Cultural detection by enrichment under aerobic conditions at 25°C[568] Charcoal cefoperazone deoxycholate agar and broth for selective identification Johnson and Murano broth[569]	

						PCR[570] SDS–PAGE[571,572] Random amplification of polymorphic DNA coupled with enterobacterial repetitive intergenic consensus PCR[573] Pulsed-field gel electrophoresis[574]	
Brucella spp.	Gram negative, aerobe, nonspore-forming, optimal growth at 37°C	Cattle, sheep, pig, goat	Raw milk and products made from unpasteurized milk	839	Acute form: 3–21 days, infrequently months Pyrexia, profuse sweats, chills, constipation, weakness, malaise, body aches, joint pains, weight loss, anorexia Chronic form: several months Long history of fever, inertia, recurrent depression, sexual impotence, insomnia Duration is weeks	Cultural methods[575] ELISA[576–578] PCR[579–582] LAMP assay[583] Lateral-flow assay[584]	Vaccination of livestock against *Brucella* spp.; avoid contact with infected animals; eradication of diseased animals; pasteurization of milk; avoid eating unpasteurized dairy products
H. pylori	Gram negative, microaerophile to anaerobe	Humans, cats	Untreated water; foodborne transmission of disease has not been proven	Unknown	Gastritis, dyspepsia, peptic ulcer, gastric carcinoma	Cultural methods[292,585] ELISA[290] Immunoassay[586,587] PCR[588,589] Rapid paper urease test[590] Oligonucleotide-based multiplex PCR[591]	Avoid contact with infected animals; use of chlorinated water for cooking and drinking

environment, including recreational or occupational visits, has been associated with *E. coli* O157:H7 infections in humans.[37,38] Since reduced fecal shedding of *E. coli* O157:H7 by cattle would potentially decrease foodborne outbreaks of *E. coli* O157:H7, a variety of approaches for decreasing the gastrointestinal carriage of *E. coli* O157:H7 in cattle have been investigated. These approaches have been focused on three important factors, namely, reduction of exposure of cattle to the pathogen, applying the pathogen exclusion principle, and implementing a direct pathogen reduction strategy.[39] *E. coli* O157:H7 can be largely controlled if sufficient hygienic measures are undertaken on farms, including providing good-quality water, feed, and housing for cattle; isolating preweaned calves from the adult herd, because calves can shed the pathogen in large numbers; and excluding nonbovine pathogen sources such as dogs, raccoons, opossums, and wild birds from farms, because they may potentially introduce *E. coli* O157:H7 to farms.[37,39–42] Avoidance of feed ingredients known to increase *E. coli* O157:H7 shedding such as barley, corn silage, and beet pulp and use of probiotics (e.g., Bovamine® that contains a mix of *Lactobacillus acidophilus* and *Propionibacterium freudenreichii*) and prebiotics are other potential strategies to exclude or reduce pathogen colonization in cattle.[39,43] Direct *E.* coli O157:H7 reduction strategies such as feeding of antimicrobial compounds, for example, sodium chlorate,[44] ionophores, neomycin, and bacteriophages, have been investigated. A recent intervention approach has emphasized vaccination of cattle against *E. coli* O157:H7 colonization, targeting intimin[45] of the type III secretion system (Bioniche®), lipopolysaccharide (LPS), and siderophore receptors[46–48] (Epitopix®) in the bacterium. In addition, a variety of postharvest interventions against *E. coli* O157:H7 have been examined, including thermal processing, high-pressure treatment, ultrasound, ionizing radiation, ozone treatment, ultraviolet light, radio waves, chemical antimicrobials, naturally occurring antimicrobial chemicals in plants, electrochemically activated water, and bacteriophages.[7]

Acidification is commonly used in food processing to control survival and growth of spoilage-causing and pathogenic microorganisms in foods. The U.S. Food and Drug Administration does not consider foods with pH ≤ 4.6 (high-acid foods) to be microbiologically hazardous for many foodborne pathogens. However, *E. coli* O157:H7 has been associated with outbreaks attributed to high-acid foods, including apple juice, mayonnaise, fermented sausage, and yogurt,[49] raising concerns about the safety of these foods. Several studies have revealed that many strains of *E. coli* O157:H7 are highly tolerant to acidic conditions, being able to survive for extended periods of time in synthetic gastric juice and in highly acidic foods.[49,50] Further, exposure of *E. coli* O157:H7 to mild or moderate acidic environments can induce an acid tolerance response, which enables the pathogen to survive extreme acidic conditions. For example, acid-adapted cells of *E. coli* O157:H7 survived longer in apple cider, fermented sausage, and hydrochloric acid than nonacid-adapted cells.[51,52] However, *E. coli* O157:H7 is not unusually heat resistant[53] or salt tolerant[54] unless cells are preexposed to acid to become acid adapted. Acid-adapted *E. coli* O157:H7 cells also have increased heat tolerance.

In humans, two principal manifestations of illness have been reported in *E. coli* O157:H7 infection. These include hemorrhagic colitis (HC) and hemolytic uremic syndrome (HUS).[55] HC is characterized by a watery diarrhea that progresses into grossly bloody diarrhea, indicative of significant amounts of gastrointestinal bleeding. Severe abdominal pain is common, but fever is usually not present. The illness typically lasts from 2 to 9 days. HUS is a severe condition, particularly among the very young and the elderly. Both these manifestations involve damage to kidneys, leading to renal failure and death. Treatment of *E. coli* O157:H7 infections with antibiotics may result in severe outcomes.[56,57] Administration of antibiotics, particularly β-lactams, is risk factor for development of HUS.[58]

The pathogenicity of EHEC is determined by virulence factors encoded by pathogenicity islands, phage chromosomes, and plasmids. The important factors attributed to the pathogenesis of *E. coli* O157:H7 include the ability of the pathogen to adhere to the intestinal mucosa of the host by the locus for enterocyte effacement (LEE) and production of Shiga toxin I (Stx1) and/or Shiga toxin II (Stx2)[35] and the large plasmid pO157.[7] The LEE encodes for an adhesion factor called intimin. Together, these factors are able to produce attaching and effacing lesions on host intestine in EHEC infections.[59] The toxins, both chromosomally and phage encoded, are produced in the colon and have the ability to reach kidneys via blood to cause HUS.[60] STEC isolates capable of producing Stx2, in particular Stx2a, are most often associated with serious disease in affected individuals than isolates that produce only Stx1.[61] The plasmid pO157, which is commonly found in most EHEC isolates, encodes for a hemolysin that is toxic to both human and bovine cells.[62] Retrospective analysis of foods implicated in outbreaks of *E. coli* O157:H7 infection suggests a low oral infectious dose of the pathogen, probably less than a hundred cells.[55]

Although infections caused by non-O157 serogroups were reported as early as 1982, a lack of reliable detection methods hindered the identification of their epidemiologic role in causing disease compared to *E. coli* O157:H7.[63] It is estimated that Shiga toxin-producing non-O157 isolates cause annually 112,750 cases with 271 hospitalizations, which account for an economic loss of $100 million.[3] Among the STEC non-O157 serogroups, serogroups O26, O45, O103, O111, O121, and O145 are leading causes of STEC inflections in the United States.[64] Recent reports suggest that the infections caused by O157 serotypes are more severe, albeit non-O157 serotypes caused significant morbidity.[65] Recently, an Stx2a-producing isolate of enteroaggregative *E. coli* O104:H4 caused a major outbreak of severe HUS and bloody diarrhea in the European Union, particularly Germany.[66] There were more than 4000 cases that included more than 900 cases of HUS and approximately 50 deaths.

Salmonella Species

Salmonella spp. are facultatively anaerobic, gram-negative, rod-shaped bacteria belonging to the family *Enterobacteriaceae*. Members of the genus *Salmonella* have an optimum growth temperature of 37°C and utilize glucose with the production of acid and gas.[67] *Salmonella* spp. are widely distributed in nature. They colonize the intestinal tract of humans, animals, birds, and reptiles and are excreted in feces, which contaminate the environment, water, and foods.[68] Many food products, especially foods having contact with animal feces, including beef, pork, poultry, eggs, milk, fruits, and vegetables, have been associated with outbreaks of salmonellosis.[69] *Salmonella* spp. can be divided into host-adapted serovars and those without any host preferences. Most of the foodborne serovars are in the latter group.

The ability of many strains of *Salmonella* to adapt to extreme environmental conditions emphasizes the potential risk of these microorganisms as foodborne pathogens. Although salmonellae optimally grow at 37°C, the genus *Salmonella* consists of strains, which are capable of growth from 5°C to 47°C.[70] *Salmonella* spp. can grow at pH values ranging from 4.5 to 7.0, with optimum growth observed near neutral pH.[68] Preexposure of *Salmonella* to mild acidic environments (pH 5.5–6.0) can induce in some strains an acid tolerance response, which enables the bacteria to survive for extended periods of exposure to acidic and other adverse environmental conditions such as heat and low water activity.[71,72] However, most *Salmonella* spp. possess no unusual tolerance to salt and heat. A concentration of 3%–4% NaCl can inhibit the growth of *Salmonella*.[73] Most salmonellae are sensitive to heat; hence, ordinary pasteurization and cooking temperatures are capable of killing the pathogen.[74]

Salmonellosis is one of the most frequently reported foodborne diseases worldwide.[75] The overall incidence of salmonellosis in the United States declined by approximately 8% during the period from 1996 to 2004.[76] However, a recent CDC study revealed that foodborne salmonellosis in the United States during the past decade has not decreased significantly.[1] Food-associated *Salmonella* infections in the United States are estimated by the U.S. Department of Agriculture to cost $3 billion annually.[77] CDC epidemiologists recently estimated 1 million cases of nontyphoidal salmonellosis annually in the United States, resulting in 19,226 hospitalizations and 378 deaths, accounting for an economic loss of $4.4 billion.[3] Among the 7564 foodborne *Salmonella* isolates serotyped in 2010 in the United States, *S*. Enteritidis was most common, followed by *S*. Newport and *S*. Typhimurium.[1] Although the overall incidence of human salmonellosis in 2005 was lower than that in the mid-1990s, the incidence of *S*. Enteritidis infections increased by approximately 25%.[78]

S. Enteritidis outbreaks are most frequently associated with the consumption of poultry products, especially undercooked eggs and chicken. Moreover, international travel especially to developing countries has been associated with human infections of *S*. Enteritidis in the United States.[79] A report from the CDC revealed 677 outbreaks of eggborne *S*. Enteritidis with 23,366 illnesses, 1,988 hospitalizations, and 33 deaths in the United States during the period 1990–2001.[80] Another study reported an estimate of 700,000 cases of eggborne salmonellosis in the United States, which accounted for approximately 47% of total foodborne salmonellosis, costing more than $1 billion annually.[81] In 2010, a nationwide outbreak of *S*. Enteritidis infection consisting of 3578 cases associated with the consumption of shell eggs was reported in the United States during the months from May to November.[82] Given that approximately 65 billion shell eggs are sold annually in the United States,[83] with a per capita consumption of approximately 254 eggs/year, *Salmonella*-contaminated eggs potentially constitute a major health hazard to humans. In light of the mounting evidence linking human salmonellosis with shell eggs, the Food and Drug Administration in 2009 announced that eggs constitute an important source of *S*. Enteritidis infections and issued a final rule that requires shell egg producers to implement measures to prevent *S*. Enteritidis from contaminating eggs on the farm and further growth during storage and transportation.

Apart from eggs, salmonellae are isolated from poultry carcasses and meat. From 1998 through 2003, the U.S. Department of Agriculture-Food Safety Inspection Service (USDA-FSIS) reported isolation of *Salmonella* from 11.2% to 22.5% of broiler and ground chicken samples, respectively.[77] In another study, White et al.[84] reported isolation of *Salmonella* from 26.4% of ground turkey, 22.5% of ground chicken, and 11.2% of broiler samples (N = 12,699/293,938 samples positive for *Salmonella*), with the largest number of *S*. Enteritidis isolates recovered from broiler carcasses.

S. Typhimurium is another significant *Salmonella* serotype causing foodborne infections worldwide.[1] A wide variety of foods, including chicken, turkey, beef, pork, peanut butter, and milk, have been associated with outbreaks caused by *S*. Typhimurium. Although the incidence of *S*. Typhimurium infections in the United States has decreased by approximately 40% during 1996–2004,[76] the emergence of *S*. Typhimurium DT 104, a new multidrug-resistant phage type in the 1990s in the United States and Europe, became a major public health concern. This is because *S*. Typhimurium DT 104 is resistant to multiple antibiotics, including ampicillin, chloramphenicol, penicillin, streptomycin, tetracycline, and sulfonamides.[85,86] A major risk factor identified in the development of *S*. Typhimurium DT 104 infection in humans was prior treatment with antimicrobial agents to which the infecting strain was resistant, during four preceding weeks of infection.[87] The CDC reported that 11% of the total *Salmonella* spp. isolated from humans in 2000 were resistant to at least five different antibiotics and a few of the multidrug-resistant strains were also resistant to gentamicin and cephalosporins.[88] These aforementioned reports underscore the prudent use of antibiotics in humans and animal husbandry.

In addition to *S*. Enteritidis and *S*. Typhimurium, several other serotypes of *Salmonella* are linked with foodborne outbreaks. These include *S*. Hadar, *S*. Newport, *S*. Virchow, and *S*. Heidelberg for which poultry meat has been a major vehicle.[89] *S*. Baildon, *S*. Braenderup, *S*. Javiana,

S. Montevideo, *S*. Newport, and *S*. Saintpaul have been associated with fresh produce-associated outbreaks.[90] A variety of pre- and postharvest strategies including competitive exclusion bacteria, bacteriophages, organic acids, prebiotic oligosaccharides, and vaccines[91–97] have been determined to help mitigate *Salmonella* contamination of chickens but with varied degrees of success rates. Recently, medium-chain fatty acids and plant-derived antimicrobials reportedly can reduce *S*. Enteritidis colonization of broiler chickens.[98,99]

In the host, *Salmonella* establishes a successful infection utilizing a variety of virulence factors, including motility, adherence to and invasion of host cells, macrophage survival, evasion of the host immune system, systemic dissemination, and finally dissemination to new hosts. Several *Salmonella* pathogenicity islands (SPI), including SPI1 and SPI2, play critical roles in the process. The pathogenicity island SPI1 controls bacterial motility, adherence, and invasion of *Salmonella* in the host's intestinal tract, whereas SPI2 regulates systemic dissemination to reach internal organs, including, for some strains such as *S*. Enteritidis, reproductive organs in chickens.[100] *Salmonella* infection in humans is characterized by fever, headache, abdominal pain, vomiting, and diarrhea and is mostly self-limiting.[101] The incubation period of the disease typically ranges from 12 to 72 h, with the illness lasting for 2–7 days. Patients usually recover within a week without any antibiotic treatment except in cases of severe diarrhea, where intravenous fluid therapy is warranted. However, severe illness caused by antibiotic-resistant strains of *S*. Enteritidis may result in an extended treatment period.[102] Vulnerable populations such as infants, children, the elderly, and immunocompromised are prone to more severe outcomes leading to an invasive disease, characterized by bacteremia and rarely death.[103] In addition, in a small percentage of affected individuals, the lingering effects of disease include chronic reactive arthritis, osteoarthritis, appendicitis, meningitis, and peritonitis.[103]

S. Typhi is the causative agent of typhoid (enteric fever), a serious human disease. Typhoid fever has a long incubation period of 7–28 days and is characterized by prolonged and spiking fever, abdominal pain, diarrhea, and headache.[67] The disease can be diagnosed by isolation of the pathogen from urine, blood, or stool specimens of affected individuals. In 2003, a total of 356 cases of typhoid fever were reported in the United States.[104] *S*. Typhi is an uncommon cause of foodborne illness in the United States, and approximately 74% of these cases reported in the United States occurred among persons who traveled internationally, especially South Asia during the preceding 6 weeks of infection.[104]

Campylobacter Species

The genus *Campylobacter* consists of 14 species; however, *C. jejuni* subsp. *jejuni* and *C. coli* are the dominant foodborne pathogens. *C. jejuni* is a slender, rod-shaped, microaerophilic bacterium that requires approximately 3%–6% oxygen for growth. It can be differentiated from *C. coli* by its ability to hydrolyze hippurate.[105] The bacterium does not survive well in the environment, being sensitive to drying, highly acidic conditions, and freezing. It is also readily killed in foods by adequate cooking.[106]

C. jejuni is one of the most commonly reported bacterial causes of foodborne infection in the United States[78,106,107] and the European Union.[108] The estimated incidence of campylobacteriosis in the United States is 13.02 per 100,000 population,[109] with an estimated 845,000 cases, 8,463 hospitalizations, and 76 deaths occurring annually.[2] Many animals, including poultry, swine, cattle, sheep, horses, and domestic pets, harbor *C. jejuni* in their intestinal tracts serving as sources of human infection. However, chickens serve as the most common reservoir of *C. jejuni*, where the bacterium primarily colonizes the mucus overlying the epithelial cells in the ceca and small intestine. L-Fucose, the major carbohydrate component present in the mucin of chicken cecal mucus, is used by *C. jejuni* as a sole substrate for growth, which gives the pathogen a competitive advantage over other competing flora for survival in the intestine.[110,111] Hence, the cecal environment in chickens is favorable for the survival and proliferation of *C. jejuni*[110] and selects for colonization of *C. jejuni* in the birds. Although a number of vehicles such as beef, pork, eggs, and untreated water have been implicated as vehicles of outbreaks of campylobacter enteritis, with chicken and unpasteurized milk being the most commonly involved foods,[112,113] epidemiologic investigations have revealed a significant link between human campylobacter infection and handling or consumption of raw or undercooked poultry meat.[113–117] Since colonization of broiler chickens by *C. jejuni* results in horizontal transmission of the pathogen and carcass contamination during slaughter, a variety of approaches for reducing its cecal carriage by chickens have been undertaken. These approaches include competitive exclusion,[94] feeding birds with bacteriophages[118,119] and acidified feed,[120] medium-chain fatty acids,[121,122] and vaccination.[123,124] In the United States, an increasing number of fluoroquinolone-resistant (e.g., ciprofloxacin) human campylobacter infections had been reported,[125] and this was attributed to the use of this antibiotic in food animal production, especially poultry.[126] Besides resistance to fluoroquinolones, strains resistant to tetracyclines and erythromycins have been recently reported.[108]

Usually campylobacter enteritis in humans is a self-limiting illness characterized by abdominal cramps, diarrhea, headache, and fever lasting up to 4 days. However, severe cases, involving bloody diarrhea and abdominal pain mimicking appendicitis, also occur.[105] Guillain–Barré syndrome (GBS) is an infrequent sequel to *Campylobacter* infection in humans.[127] GBS is characterized by acute neuromuscular paralysis[106] and is estimated to occur in approximately one of every 1000 cases of campylobacter enteritis.[128] A few strains of *C. jejuni* reportedly produce a heat-labile enterotoxin similar to that produced by *Vibrio cholera*e and ETEC.[105] Some strains of *C. jejuni* and *C. coli* can also produce a cytolethal distending toxin, which causes a rapid and specific cell cycle arrest in HeLa and Caco-2 cells.[129]

Shigella Species

Shigella is a common cause of human diarrhea in the United States. The genus *Shigella* is divided into four major groups: *S. dysenteriae* (group A), *S. flexneri* (group B), *S. boydii* (group C), and *S. sonnei* (group D) based on the organism's somatic (O) antigen. Although all the four groups have been involved in human infections, *S. sonnei* accounts for more than 75% of shigellosis cases in humans[130] and has been linked to persistent infections in community and day-care centers.[131–133] Humans are the natural reservoirs of *Shigella* spp. The fecal–oral route is the primary mode of transmission of Shigellae and proper personal hygiene and sanitary practices of cooks and food handlers can greatly reduce the occurrence of outbreaks of shigellosis. Most foodborne outbreaks of shigellosis are associated with ingestion of foods such as salads and water contaminated with human feces containing the pathogen. Shigellosis is characterized by diarrhea containing bloody mucus, which lasts 1–2 weeks. The infectious dose for *Shigella* infection is low. The ID_{50} of *S. flexneri* and *S. sonnei* in humans is approximately 5000 microorganisms and that of *S. dysenteriae* is a few hundred cells; hence, secondary transmission of *Shigella* by person-to-person contact frequently occurs in outbreaks of foodborne illness. The incidence of shigellosis has decreased significantly during the 1996–2010 surveillance period,[1] although it is estimated to cause an economic loss of $257 million annually.[3] An emerging serotype of *S. boydii*, namely, serotype 20, has been reported in the United States.[134]

Yersinia enterocolitica

Yersinia enterocolitica is a gram-negative, rod-shaped, facultative anaerobic bacterium, which was first isolated and described during the 1930s.[135] Swine have been identified as an important reservoir of *Y. enterocolitica*, in which the pathogen colonizes primarily the buccal cavity.[136] Although pork and pork products are considered to be the primary vehicles of *Y. enterocolitica*, a variety of other foods, including milk, ice cream, beef, lamb, seafood, and vegetables, have been identified as vehicles of *Y. enterocolitica* infection.[137] One of the largest outbreaks of yersiniosis in the United States was associated with milk.[138] Water has also been a vehicle of several outbreaks of *Y. enterocolitica* infection.[138] Surveys have revealed that *Y. enterocolitica* is frequently present in foods, having been isolated from 11% of sandwiches, 15% of chilled foods, and 22% of raw milk in Europe.[139] Several serovars of pathogenic *Y. enterocolitica* have been reported, which include O:3, O:5, O:8, and O:9,[140–142] with serovar O:3 (bioserotype 4) being the most common causing human disease in the United States.[105–107] Although the incidence of *Yersinia* infection from 1996 to 2010 has decreased by 52% compared to the 1996–1998 surveillance period,[1] the pathogen causes annually an estimated 97,700 cases, 533 hospitalizations, and 29 deaths, accounting for $400 million loss.[3]

In addition to foodborne outbreaks, reports of blood transfusion-associated *Y. enterocolitica* sepsis indicate another potential mode of transmission of this pathogen.[143,144] Among bacteria, *Y. enterocolitica* has emerged as a significant cause of transfusion-associated bacteremia and mortality (53%), with 49 cases reported since this condition was first documented in 1975.[145] A review of these cases revealed that bacteremia may occur in a subpopulation of individuals with *Y. enterocolitica* gastrointestinal infection.[140] The strains of *Y. enterocolitica* responsible for transfusion-acquired yersiniosis are the same serobiotypes as those associated with enteric infections.

An unusual characteristic of *Y. enterocolitica* that influences food safety is its ability to grow at low temperatures, even as low as −1°C.[146] *Y. enterocolitica* readily withstands freezing and can survive in frozen foods for extended periods, even after repeated freezing and thawing.[147] Refrigeration (4°C) is one of the common methods used in food processing to control growth of spoilage and pathogenic microorganisms in foods. However, several studies have revealed growth of *Y. enterocolitica* in foods stored at refrigeration temperature. *Y. enterocolitica* grew on pork, chicken, and beef at 0°C–1°C.[148,149] The psychrotrophic nature of *Y. enterocolitica* also poses problems for the blood transfusion industry, mainly because of its ability to proliferate and release endotoxin in blood products stored at 4°C without manifesting any alterations in their physical appearance. The ability of *Y. enterocolitica* to grow well at refrigeration temperature has been exploited for isolating the pathogen from foods, water, and stool specimens. Such samples are incubated at 4°C–8°C in an enrichment broth for several days to selectively culture *Y. enterocolitica* based on its psychrotrophic nature.

Y. enterocolitica is primarily an intestinal pathogen with a predilection for extraintestinal spread under appropriate host conditions such as immunosuppression. In the gastrointestinal tract, *Y. enterocolitica* can cause acute enteritis, enterocolitis, mesenteric lymphadenitis, and terminal ileitis often mimicking appendicitis.[140] In the intestinal tract, the pathogen employs major virulence determinants such as invasins (Inv)—the proteins that mediate binding to host cell integrins, attachment invasion locus (Ail)—an outer-membrane protein associated with adhesion and invasion of the pathogen, a high-pathogenicity island (HPI) that sequesters iron, and a virulence plasmid (pVY) that encodes for YadA and Yop proteins for increased pathogenicity.[142] Infection with *Y. enterocolitica* often leads to secondary, immunologically induced sequelae such as arthritis (most common), erythema nodosum, Reiter's syndrome, glomerulonephritis, and myocarditis.

Vibrio Species

Seafoods form a vital part of the American diet, and their consumption in the United States has risen steadily over the past few decades from an average of 4.5 kg/person in 1960 to about 7 kg in 2002.[150,151] However, according to a recent report published by the CSPI, contaminated seafoods have been recognized as a leading known cause of most foodborne illness outbreaks in the United States.[152] Vibrios, especially *V. parahaemolyticus*, *V. vulnificus*, and *V. cholerae*, which are commonly associated with estuarine and marine waters,

represent the major pathogens resulting in disease outbreaks through consumption of seafoods and cause severe infections in cirrhotic patients.[153] The CDC reported a 115% increase in *Vibrio* infections during 1996–2010.[1] In addition, a recent epidemiologic investigation revealed that *Vibrio* spp. cause an estimated 34,800 cases with 195 hospitalizations and 40 deaths annually, accounting for $336 million in losses. However, among the vibrios, *V. vulnificus* caused the greatest economic impact, accounting for a loss of $268 million. *V. parahaemolyticus* and *V. vulnificus* are halophilic in nature, requiring the presence of 1%–3% sodium chloride for optimum growth. *V. cholerae* can grow in media without added salt, although their growth is stimulated by the presence of sodium ions.

Among the three species of *Vibrio*, *V. parahaemolyticus* accounts for the largest number of foodborne disease outbreaks (it was responsible for 34,664 of the total 34,844 cases reported for *Vibrio* spp.).[3] *V. parahaemolyticus* is present in coastal waters of the United States and the world. *V. parahaemolyticus* being an obligate halophile can multiply in substrates with sodium chloride concentrations ranging from 0.5% to 10%, with 3% being the optimal concentration for growth. The ability of *V. parahaemolyticus* to grow in a wide range of salt concentrations reflects on its existence in aquatic environments with various salinities. *V. parahaemolyticus* has a remarkable ability for rapid growth, and generation times as short as 12–18 min in seafoods have been reported at 30°C. Growth rates at lower temperatures are slower, but counts were found to increase from 10^2 to 10^8 colony-forming units (CFU)/g after 24 h storage at 25°C in homogenized shrimp and from 10^3 to 10^8 CFU/g after 7 days of storage at 12°C in homogenized oysters.[154] Because of its rapid growth, proper refrigeration of cooked seafoods to prevent regrowth of the bacterium is critical to product safety. A survey by the U.S. Food and Drug Administration revealed that 86% of 635 seafood samples contained *V. parahaemolyticus*, being isolated from codfish, sardine, mackerel, flounder, clam, octopus, shrimp, crab, lobster, crawfish, scallop, and oyster.[155] The pathogen has been a major seafood-associated *Vibrio* in Asian countries, including Japan, Taiwan, and China.[156] A new serotype of *V. parahaemolyticus*, O3:K6, that emerged in the Southeast Asia in the 1990s has been implicated in oyster-related outbreaks in the United States in 1997 and 1998.[157] An important virulence characteristic of pathogenic strains of *V. parahaemolyticus* is their ability to produce a thermostable hemolysin (Kanagawa hemolysin).[158] Studies in humans on the infectious dose of pathogenic *V. parahaemolyticus* strains revealed that ingestion of approximately 10^5–10^7 bacteria can cause gastroenteritis.[155]

Among the 206 serogroups of *V. cholerae* identified thus far, serogroups O1 and O139, the causative agents of cholera in humans, are a part of the normal estuarine microflora, and foods such as raw fish, mussels, oysters, and clams have been associated with outbreaks of cholera.[159] The clinical course of cholera, which is a toxin-mediated acute illness, results in severe diarrhea. The bacterium secretes an enterotoxin that binds to receptors on the epithelial cell membrane of the small intestine causing increased levels of cAMP. Subsequently, elevated secretion of fluid and electrolytes results in a characteristic "rice water" diarrhea with large amounts of mucus in the stools.[153] The presence of a type VI secretion system (T6SS) in *V. cholerae* involved in its pathogenesis was recently identified.[160] Infected humans can serve as short-term carriers, shedding the pathogen in feces. Cholera is characterized by profuse diarrhea, potentially fatal in severe cases, and often described as "rice water" diarrhea due to the presence of prolific amounts of mucus in the stools. Gastroenteritis caused by non-O1 and non-O139 serovars of *V. cholerae* is usually mild in nature. During the period from 1996 to 2005, a total of 64 cases of toxigenic *V. cholerae* O1 were reported in the United States, of which 35 (55%) cases were acquired during foreign travel and 29 (45%) cases were domestically acquired.[161] Seven (24%) of the 29 domestic cases were attributed to consumption of Gulf Coast seafood (crabs, shrimp, or oysters). Moreover, seven of the eleven domestic cholera cases in 2005 were reported during October–December, after Hurricanes Katrina and Rita, although no evidence suggests increased risk for cholera among Gulf Coast residents or consumers of Gulf Coast seafood after the hurricanes. In 2003, a total of 111,575 cases of cholera worldwide were reported to the World Health Organization from 45 countries.[162]

V. vulnificus is the most serious of the vibrios and is responsible for most of the seafood-associated deaths in the United States, especially in Florida.[155] *V. vulnificus* results in life-threatening bacteremia, septicemia, and necrotizing fasciitis in persons with liver disorders and high iron level in blood, diabetes mellitus, end-stage renal disorders, and immunodeficiency conditions.[163] Although a number of seafoods have been associated with *V. vulnificus* infection, raw oysters are the most common vehicle associated with cases of illness.[164] The major virulence factors responsible for causing sepsis and bacteremia in *V. vulnificus* include its ability to escape acidic conditions in the stomach and its expression of capsular polysaccharide and surface LPSs, cytotoxins, pili, and flagella.[165]

Cronobacter sakazakii

Cronobacter sakazakii, formerly *Enterobacter sakazakii*, is a foodborne pathogen that causes severe meningitis, meningoencephalitis, sepsis, and necrotizing enterocolitis in neonates and infants, with a case fatality rate of 40%–80%.[159–163] *C. sakazakii* infections may also result in severe neurological sequelae such as hydrocephalus, quadriplegia, and retarded neural development in survivors.[166] The epidemiology and reservoir of this pathogen are still unknown and most strains have been isolated from clinical specimens such as cerebrospinal fluid, blood, skin, wounds, urine, and respiratory and digestive tract samples.[167] The bacterium has also been isolated from foods such as cheese, eggs, fish, pork, shellfish, sausage, barley, biscuits, cowpea paste, nuts, seeds, rice, soy, sweets, tea, minced beef, sausage, and vegetables, namely, salads and tomato.[168,169] Recently, Kandhai et al.[170,171] isolated *C. sakazakii* from household and food production

facility environmental samples, such as scrapings from dust, vacuum cleaner bags, and spilled product near equipment, and proposed that the organism could be more widespread in the environment than previously thought. Although the environmental source of *C. sakazakii* has not been identified, epidemiologic studies implicate dried infant formula as the primary route of transmission to infants.[172–175] The bacterium has been isolated from powdered infant formula by numerous investigators.[174,176–178] Muytjens et al.[178] isolated the pathogen from powdered infant formula from 35 different countries.

C. sakazakii possesses several characteristics that enable it to grow and survive in infant formula. For example, the pathogen can grow at temperatures as low as 5.5°C,[179] which is within the temperature range of many home refrigerators.[180] A study on the thermal resistance of *C. sakazakii* in reconstituted infant formula indicated that it is one of most thermotolerant bacteria under *Enterobacteriaceae*.[181] A recent study by Breeuwer et al.[182] reported that *C. sakazakii* also has a high tolerance to osmotic stress and desiccation. In addition, *C. sakazakii* possesses a short lag time and generation time in reconstituted infant formula,[179] raising concerns that improper storage of reconstituted formula may permit its substantial growth. Recently, Iversen and Forsythe[183] reported the isolation of *C. sakazakii* from a variety of foods, including powdered infant formula, dried infant food and milk powder, as well as certain herbs and spices. The first case of neonatal meningitis caused by *C. sakazakii* was reported in 1958,[184] and since then a number of *C. sakazakii* infections have been reported worldwide, including the United States. In the United States, an outbreak of *C. sakazakii* involving four infants occurred in the neonatal intensive care unit of a hospital in Memphis, resulting in sepsis, bloody diarrhea, and intestinal colonization. The source of infection was traced to contaminated infant formula.[174] In 2002, Himelright et al.[185] reported a case of fatal neonatal meningitis caused by *C. sakazakii* in Tennessee, associated with feeding of contaminated infant formula. The infection occurred in the neonatal intensive care unit of a hospital and surveillance studies identified two more cases of suspected infection with positive stool or urine in seven more infants. There were many recalls of *C. sakazakii*-contaminated infant formula in the United States. In November 2002, a nationwide recall of more than 1.5 million cans of dry infant formula contaminated with *C. sakazakii* was reported.[186] Besides survival and growth in several foods including reconstituted infant formula, *C. sakazakii* is a good biofilm former on abiotic surfaces such as latex, silicon and stainless steel, and neonatal nasogastric feeding tubes.[187] The International Commission on Microbiological Specification for Foods classified *C. sakazakii* as "severe hazard for restricted populations, life-threatening or substantial chronic sequelae of long duration." This places *C. sakazakii* in the same category as other serious food- and waterborne pathogens such as *Listeria monocytogenes*, *Clostridium botulinum* types A and B, and *Cryptosporidium parvum*.[188]

The most common clinical manifestations of infections due to *C. sakazakii* are sepsis and meningitis in neonates. In more than 90% of the cases reported, patients developed meningitis with a very high prevalence for developing brain abscesses and less frequently ventriculitis and hydrocephalus.[189,190] While the reported mortality rates of *C. sakazakii* infections in neonates have declined over time from 50% or more to less than 20% due to advances in antimicrobial chemotherapy, an increasing incidence of resistance to commonly used antibiotic necessitates a reevaluation of existing treatment strategies.[167] Biering et al.[176] indicated that besides the high rate of mortality, the CNS infections due to *C. sakazakii* often lead to permanent impairment in mental and physical capabilities in surviving patients. In addition to meningitis, *C. sakazakii* is also reported to cause necrotizing enterocolitis in neonates and bacteremia, osteomyelitis, and pneumonia in elderly adults.[172,191–193]

Aeromonas hydrophila

Although *Aeromonas* species have been recognized as pathogens of cold-blooded animals, their potential to cause human infections, especially foodborne illness, received attention only recently. *A. hydrophila* has been isolated from drinking water, fresh and saline waters, and sewage.[194] It also has been isolated from a variety of foods such as fish, oyster, shellfish, raw milk, ground beef, chicken, and pork.[194] *A. hydrophila* was isolated from cultured channel catfish, *Ictalurus punctatus*, during a disease outbreak in West Alabama in 2009.[195] Although *A. hydrophila* is sensitive to highly acidic conditions and does not possess any unusual thermal resistance, some strains are psychrotrophic and grow at refrigeration temperature.[196] *A. hydrophila* can grow on a variety of refrigerated foods, including pork, asparagus, cauliflower, and broccoli.[197,198] However, considering the widespread occurrence of *A. hydrophila* in water and food and its relatively infrequent association with human illness, it is likely that most strains of this bacterium are not pathogenic for humans. *A. hydrophila* infection in humans is characterized by watery diarrhea and mild fever. Virulent strains of *A. hydrophila* produce a 52 kDa polypeptide, which possesses enterotoxic, cytotoxic, and hemolytic activities.[199] *A. hydrophila* strains with resistance to multiple antibiotics have been reported.[200]

Plesiomonas shigelloides

Plesiomonas shigelloides has been implicated in several cases of sporadic and epidemic gastroenteritis[201] and is regarded as an emerging enteric pathogen in humans.[202] The pathogen is present in fresh and estuarine waters and has been isolated from various aquatic animals.[196] Seafoods such as fish, crabs, and oysters have been associated with cases of *P. shigelloides* infection. The isolation of *P. shigelloides* from vertebrate animals, including swine, cats, dogs, and monkeys, suggests its potential for being a zoonotic pathogen.[202] The most common symptoms of *P. shigelloides* infection include abdominal pain, nausea, chills, fever, and diarrhea. Potential virulence factors of *P. shigelloides* include cytotoxic enterotoxin, invasins, and β-hemolysin.[196] An outbreak of *P. shigelloides*

infection associated with drinking well water and involving 30 persons was reported in New York in 1996.[203]

Listeria monocytogenes

L. monocytogenes has emerged into a highly significant and fatal foodborne pathogen throughout the world, especially in the United States. There is an estimated 2500 cases of listeriosis annually in the United States, with a mortality rate of ca. 25%.[204] Further, *L. monocytogenes* is of tremendous economic significance, causing an estimated monetary loss of $2.3 billion annually in the United States.[205] A large outbreak of listeriosis involving more than 100 cases and associated with eating contaminated turkey frankfurters occurred during 1998–1999.[206] During this period of time, there were more than 35 recalls of a number of different food products contaminated with listeriae.[206] In 2002, a large outbreak of listeriosis in the United States involving 46 people, 7 deaths, and 3 miscarriages resulted in a recall of 27.4 million pounds of fresh and frozen ready-to-eat chicken and turkey frankfurters.[88] In 2003, 696 cases of listeriosis were reported in the United States, with more than 50% of the cases occurring in persons above 60 years of age.[104] Contaminated ready-to-eat meat was implicated as the vehicle of two large multiprovince *Listeria* outbreaks that occurred in Canada in 2008.[207] In the same year in Austria, contaminated jellied pork was the vehicle of invasive listeriosis characterized by febrile gastroenteritis.[208] In 2011, a nationwide outbreak of listeriosis in the United States, involving more than 130 people with 30 deaths and one abortion, was associated with consumption of contaminated cantaloupe.[1]

L. monocytogenes is widespread in nature, occurring in soil, vegetation, and untreated water. Humans and a wide variety of farm animals, including cattle, sheep, goat, pig, and poultry, are known sources of *L. monocytogenes*.[209] *L. monocytogenes* also occurs frequently in food processing facilities, especially in moist areas such as floor drains, floors, and processing equipment.[210] *L. monocytogenes* can also grow in biofilms attached to a variety of processing plant surfaces such as stainless steel, glass, and rubber.[211] A wide spectrum of foods, including milk, cheese, beef, pork, chicken, seafoods, fruits, and vegetables, has been identified as vehicles of *L. monocytogenes*.[209] However, ready-to-eat cooked foods such as low-acid soft cheese, pâtes, and cooked poultry meat, which can support the growth of listeriae to large populations (>10^6 cells/g) when held at refrigeration temperature for several weeks, have been regarded as high-risk foods.[212,213] *L. monocytogenes* possesses several characteristics, which enable the pathogen to successfully contaminate, survive, and grow in foods, thereby resulting in outbreaks. These traits include an ability to grow at refrigeration temperature and in a medium with minimal nutrients; ability to survive in acidic conditions, e.g., pH 4.2; ability to tolerate up to 10% sodium chloride; ability to survive incomplete cooking or subminimal pasteurization treatments; and ability to survive in biofilms on equipment in food processing plants and resist superficial cleaning and disinfection treatments.[206]

Approximately 3%–10% of humans carry listeriae in their gastrointestinal tract with no symptoms of illness.[214] Human listeriosis is an uncommon illness with a high mortality rate. The infection most frequently occurs in people who are older, pregnant, or possess a compromised immune system. Clinical manifestations range from mild influenza-like symptoms to meningitis and meningoencephalitis. Pregnant females infected with the pathogen may not present symptoms of illness or may exhibit only mild influenza-like symptoms. However, spontaneous abortion, premature birth, and stillbirth are frequent sequelae to listeriosis in pregnant females.[213] Although the infective dose of *L. monocytogenes* is not known, published reports indicate that it is likely to be more than 100 CFU per gram of food.[213] However, the infective dose largely depends on the age, condition of health, and immunological status of the host.

L. monocytogenes crosses the intestinal barrier in hosts infected by the oral route. However, before reaching the intestine, the bacterium must withstand the adverse environment of the stomach. Gastric acidity may destroy a significant number of *L. monocytogenes* ingested with contaminated food. The site at which intestinal translocation of *L. monocytogenes* occurs is not clearly elucidated. However, both epithelial cells and M cells in the Peyer's patches are believed to be the potential sites of entry.[215] The bacteria are then internalized by macrophages where they survive and replicate. This is followed by the transport of the pathogen via blood to the mesenteric lymph nodes, spleen, and the liver. The primary site of *L. monocytogenes* replication in the liver is the hepatocyte. In the initial phase of infection, the infected hepatocytes are the target for neutrophils and subsequently for mononuclear phagocytes, which aid the control and resolution of the infection.[213] If the immune system fails to contain *L. monocytogenes*, subsequent propagation of pathogen via blood to the brain or uterus takes place.[216] The major virulence factors in *L. monocytogenes* include hemolysin, phospholipases, metalloprotease, Clp proteases and ATPases, internalins, surface protein p104, protein p60, listeriolysin O, and the surface protein *ActA*.[213]

Staphylococcus aureus

Recent epidemiologic estimates indicate 241,000 cases of *S. aureus*-related illnesses, resulting in 1,064 hospitalizations and 6 deaths annually in the United States, which account for a loss of $130 million.[3] Preformed, heat-stable enterotoxin that can resist boiling for several minutes is the agent responsible for staphylococcal food poisoning. Among these, enterotoxin A is the most common cause of food poisoning episodes.[217] Humans are the principal reservoir of *S. aureus* strains involved in outbreaks of foodborne illness. In addition, a recent study revealed that *S. aureus* can be transmitted between healthy, lactating mothers without mastitis and their infants by breastfeeding.[218] Colonized humans can be long-term carriers of *S. aureus* and thereby contaminate foods and other humans.[219] The organism commonly resides in the throat and nasal cavity and on the skin, especially in boils and carbuncles.[219]

Staphylococcal protein A (*Spa*) typing and DNA microarray have revealed striking similarities between the nasal isolates of food handlers and isolates involved in outbreaks.[220] Protein-rich foods such as ham, poultry, fish, dairy products, custards, cream-filled bakery products, and salads containing cooked meat, chicken, and potatoes are the vehicles most frequently associated with *S. aureus* food poisoning.[221] Additionally, other food vehicles, including hamburgers, milk, pasta salad, and raw milk cheese, have been implicated in *S. aureus* food poisoning.[222] *S. aureus* is usually overgrown by competing bacterial flora in raw foods; hence, raw foods are not typical vehicles of staphylococcal food poisoning. Cooking eliminates most of the normal bacterial flora of raw foods, thereby enabling the growth of *S. aureus*, which can be introduced by infected cooks and food handlers into foods after cooking. The incubation period of staphylococcal food poisoning is very short, with symptoms being observed within 2–6 h after eating toxin-contaminated food. Symptoms include nausea, vomiting, diarrhea, and abdominal pain.

S. aureus can grow within a wide range of pH values from 4 to 9.3, with optimum growth occurring at pH 6–7. *S. aureus* has an exceptional tolerance to sodium chloride, being able to grow in foods in the presence of 7%–10% NaCl, with some strains tolerating up to 20% NaCl.[221] *S. aureus* has the unique ability to grow at a water activity as low as 0.83–0.86.[223] *S. aureus* produces nine different enterotoxins, which are quite heat resistant, losing their serological activity at 121°C but not at 100°C for several minutes.[223]

Besides being a foodborne pathogen, *S. aureus* has emerged as an important pathogen in nosocomial infections and community-acquired diseases, because of its toxin-mediated virulence, invasiveness, and antibiotic resistance.[224] This is especially significant due to the emergence of methicillin-resistant strains of *S. aureus* (MRSA), and 50% of healthcare-acquired *S. aureus* isolates in the United States in 1997 were methicillin resistant.[225] Although MRSA are commonly linked to nosocomial infections, the first report of MRSA-associated foodborne disease in a community was reported in 2002.[225] The community-acquired MRSA are particularly virulent, resulting in tissue destructing infections, necrotizing fasciitis, and fulminant pneumonia, and this is attributed to a factor called Panton–Valentine leukocidin (PVL).[226] In addition, the gene responsible for methicillin resistance, *mecA*, encodes a low-affinity penicillin-binding protein called PBP2a that confers resistance to not only methicillin but also to the entire class of β-lactam antibiotics such as cephalosporins, penicillins, and carbapenems.[226] Some clones of MRSA are colonizers of the pig intestinal tract, and recent reports reveal that pig-to-human transmission is possible, highlighting its zoonotic potential.[227,228] Researchers have observed an expanding spectrum of antibiotic resistance in MRSA, with emerging linezolid resistance in MRSA strains.[229]

Clostridium botulinum

Foodborne botulism is an intoxication caused by ingestion of foods containing preformed botulinal toxin, a 150 kDa metalloprotease produced by *C. botulinum* under anaerobic conditions. Botulinal toxin is a neurotoxin, which causes the neuroparalytic disease called botulism. The genes encoding botulinum toxins and other related proteins are located together in a cluster found on the *C. botulinum* chromosome or plasmid. There are two conserved cluster types in *C. botulinum*: the "ha cluster" and the "orf-X cluster."[230] The toxin binds irreversibly to the presynaptic nerve endings of the nervous system, where it inhibits the release of acetylcholine. Unlike botulism in adults, infant botulism results from the colonization and germination of *C. botulinum* spores in the infant's gastrointestinal tract. The disease usually happens in infants during the second month of age and is characterized by constipation, poor feeding or sucking, and decreased muscle tone with a "floppy" head.[231] Although the source of infection is unknown in majority of the cases, most commonly suspected food in infant botulism is honey.[232]

There are seven types of *C. botulinum* (A, B, C, D, E, F, and G) classified on the basis of the antigenic specificity of the neurotoxin they produce.[233] The organism is present in soil, vegetation, and sedimentation under water. Type A strains are proteolytic, whereas type E strains are nonproteolytic.[234] Another classification divides *C. botulinum* into four groups: group 1 (type A strains and proteolytic strains of types B and F), group II (type E strains and nonproteolytic strains of B and F), group III (type C and D strains), and group IV (type G strains). The association of *C. botulinum* types I–III in disease outbreaks in cattle has raised concerns regarding the potential transmission of the toxin to humans via dairy products.[235]

Type A *C. botulinum* occurs frequently in soils of the western United States, whereas type B strains are more often present in the eastern states and in Europe.[234] Type E strains are largely associated with aquatic environments and fish. Type A cases of botulism in the United States are frequently associated with temperature-abused, home-prepared foods. Proteolytic type A, B, and F strains produce heat-resistant spores, which pose a safety concern in low-acid canned foods. In contrast, nonproteolytic type B, E, and F strains produce heat-labile spores, which are of concern in pasteurized or unheated foods.[234] The minimum pH for growth of group I and group II strains is 4.6 and 5, respectively.[233] Group I strains can grow at a minimum water activity of 0.94, whereas group II strains do not grow below a water activity of 0.97.[236] The proteolytic strains of *C. botulinum* are generally more resistant to heat than nonproteolytic strains.

Types of foods associated with cases of botulism include fish, meat, honey, soup, chilli sauce, baked potato, sausage, tofu, and home-canned vegetables.[230,233,237] Several other vehicles such as poultry litter, water, water fowls, silage, brewer's grain, bakery waste, and cat and cattle carcasses have also been implicated in botulism outbreaks during the past three decades.[235] In September 2011, two cases of botulism were associated with ground green olive paste in France.[238]

Clostridium perfringens

C. perfringens is a major bacterial cause of foodborne disease, with 1062 cases reported in the United States in 2004.[8] *C. perfringens* strains are grouped into five types: A, B, C, D, and E, based on the type(s) of toxin(s) produced. *C. perfringens* foodborne illness is almost exclusively associated with type A isolates of *C. perfringens* that carry the plasmid-borne *C. perfringens* enterotoxin (cpe) gene.[239] This toxin type causes gangrene in humans and severe enteric disease in humans and animals.[240] *C. perfringens* is commonly present in soil, dust, water, and in the intestinal tract of humans, animals, and birds.[241] It is frequently present in foods; about 50% of raw or frozen meat and poultry contain *C. perfringens*.[242] Spores produced by *C. perfringens* are quite heat resistant and can survive boiling for up to 1 h.[242] *C. perfringens* spores can survive in cooked foods, and if not properly cooled before refrigerated storage, the spores will germinate and vegetative cells can grow to large populations during holding at growth temperatures. Large populations of *C. perfringens* cells (>10^6/g) ingested with contaminated food will enter the small intestine, multiply, and sporulate. During sporulation in the small intestine, *C. perfringens* enterotoxin is produced, which induces a diarrheal response. The enterotoxin is a 35 kDa heat-labile polypeptide that damages the epithelial cells of the gastrointestinal tract to cause fluid and electrolyte loss.[243,244] Although vegetative cells of *C. perfringens* are sensitive to cold temperature and freezing, spores tolerate cold temperature well and can survive in refrigerated foods.

Clostridium difficile

Clostridium difficile is a major cause of enteric disease in humans, and recent evidence indicates that it has emerged into a community-associated pathogen. *C. difficile* has been isolated from the intestinal tract of many food animals,[245,246] and several small-scale studies conducted in different parts of the world have revealed the presence of *C. difficile* in retail meat and meat products.[247,248] This has raised concerns that foods could potentially be involved in the transmission of *C. difficile* to humans.

C. difficile is a gram-positive, spore-forming, anaerobic bacterium, which causes a toxin-mediated enteric disease in humans.[249] The total annual number of cases of *C. difficile* infection in the United States is estimated to exceed 250,000,[250] resulting in approximately U.S. $1 billion annually in health-care costs. Among patients diagnosed with *C. difficile* infection, relapse or reinfection occurs in 12%–24% within 2 months.[251] Moreover, the mortality rates of disease associated with *C. difficile* in the United States have increased from 5.7 per million to 23.7 per million from 1999 to 2004, respectively.[252] The symptoms in *C. difficile* disease include abdominal pain, fever, fulminant colitis, toxic megacolon (bowel perforation), sepsis, and shock.[245] In addition, asymptomatic colonization of *C. difficile* causing mild diarrhea has been reported in some patients. *C. difficile* infection has been associated with the use of gastric acid-suppressing agents and antibiotics, which result in the germination of spores in the stomach and selection for *C. difficile* in the intestine.[253]

Historically, *C. difficile* was considered a nosocomial pathogen that mainly affected the elderly, the severely ill, and the long-term hospital inpatients.[254] However, recently some changes in the epidemiology of *C. difficile* have been reported. For example, an increase in community-acquired *C. difficile*-associated disease (CDAD) has been reported, especially in populations that were not previously considered at risk of infection.[254] Another change in the epidemiology of *C. difficile* is that an increase in morbidity, mortality, and relapse rate in infections has been reported in the United States and elsewhere, which is attributed to the emergence and dissemination of a new hypervirulent strain, classified as North American Pulse type 1(NAP 1) using pulsed-field gel electrophoresis.[245,249] The strain belongs to the toxin type III and ribotype 027.[255] Emerging antimicrobial resistance in *C. difficile* has been reported by many investigators, especially resistance to fluoroquinolones, clindamycin and erythromycin, metronidazole, vancomycin, gatifloxacin, and moxifloxacin.[256]

The major virulence factors of *C. difficile* include two large toxins, namely, toxin A (TcdA, enterotoxin) and toxin B (TcdB, cytotoxin).[257] In addition, a third toxin called *C. difficile* binary toxin (CDT) has been detected in some strains of the pathogen.[258] TcdA and TcdB are encoded by two genes present in a single operon and are highly expressed during late log and stationary phases of growth upon exposure to environmental stimuli.[259] The binary toxin was detected in approximately 6% of clinical *C. difficile* isolates obtained from the United States and Europe,[260] and an increase in the prevalence of binary toxin-producing *C. difficile* strains has been reported during the last decade.[255,261]

The common means of contracting *C. difficile* infection in humans is via the fecal–oral route. The bacterium is ingested in the vegetative form or as spores, which can persist for long periods in the environment and overcome the acidity in the stomach. In the intestine, *C. difficile* spores germinate into the vegetative form, especially if the normal flora has been disrupted by antibiotic therapy. *C. difficile* multiplies in the intestinal crypts, releasing the A and B toxins, causing severe inflammation and disruption of intestinal epithelial cells, thereby leading to colitis, pseudomembrane formation, and watery diarrhea.[251]

Recent studies conducted worldwide have revealed the occurrence of *C. difficile* in a variety of food animals.[246,262] Pigs and calves are among the most common reservoirs of *C. difficile*. Apart from animals serving as reservoirs, foods such as ground beef, ground veal, veal chops, retail chicken (thighs, wings, and legs), raw milk, summer sausage, ground pork, ground turkey, braunschweiger, water, and raw vegetable samples have been identified as potential vehicles of *C. difficile*.[247,248,263]

Bacillus cereus

B. cereus is a spore-forming pathogen present in soil and on vegetation. It is responsible for an increasing number of

foodborne diseases in industrial countries,[264] with 103 outbreak-associated confirmed cases reported in the United States in 2004.[8] It is reported as the fourth largest cause of foodborne disease in the European Union.[265] It is frequently isolated from foods such as meat, spices, vegetables, dairy products, and cereal grains, especially fried rice.[266] There are two types of foodborne illness caused by *B. cereus*, i.e., a diarrheagenic illness and an emetic syndrome.[264,267] The diarrheal syndrome caused by heat-labile enterotoxins is usually mild and is characterized by abdominal cramps, nausea, and watery stools similar to that observed in *C. perfringens* infection.[268] Types of foods implicated in outbreaks of diarrheal syndrome include cereal food products containing corn and corn starch, mashed potatoes, vegetables, milk, and cooked meat products. The emetic syndrome is caused by a heat-stable dodecadepsipeptide toxin called cereulide that is produced in food[264] and is characterized by severe vomiting. The clinical symptoms are similar to those observed in *S. aureus* poisoning.[269] Refried or rewarmed boiled rice, pasta, noodles, ice cream, and pastry are frequently implicated in outbreaks of emetic syndrome.[270,271] The dose of *B. cereus* required to produce diarrheal illness is estimated at more than 10^5 cells/g.[272] The toxin-induced pathogenicity of *B. cereus* is regulated by a pleiotropic transcriptional activator, PlcR, that controls the production of enterotoxins—hemolytic Hbl and nonhemolytic Nhe—and the cytotoxin CytK.[273,274]

Arcobacter butzleri

Arcobacter species belong to the family of *Campylobacteraceae* and occur primarily as commensals in the gut of animals and humans.[275] Arcobacters are Gram-negative, aerotolerant *Campylobacter*-like organisms that can grow under microaerobic conditions.[276] There are 13 species of *Arcobacter*, of which *A. butzleri*, *A. cryaerophilus*, and *A. skirrowii* are of public health importance.[277] They can grow at 25°C, a differentiating feature from *Campylobacter*, and can hydrolyze indoxyl acetate and reduce nitrate.[278] Although *Arcobacter* can grow at a range of 15°C–37°C, the optimum temperature for growth is 30°C.[279] Among the arcobacters, *A. butzleri* is most commonly associated with human enteritis, characterized by persistent and watery diarrhea, vomiting, nausea, and fever.[280] *A. butzleri* strains resistant to antibiotics such as clindamycin, ciprofloxacin, metronidazole, carbenicillin, cefoperazone, nalidixic acid, and azithromycin have been reported.[277]

A. butzleri is the most common *Arcobacter* isolated from livestock species. There is mounting evidence that arcobacters in general, and *A. butzleri* in particular, are efficient colonizers in healthy swine, sheep, horses, and cattle,[281] with poultry being the most significant reservoir. However, there are conflicting reports on the pathogen's role as a commensal in the chicken intestinal tract.[282] Humans may contract *Arcobacter* infection via consumption of contaminated food of animal origin and water,[277] although this is not fully understood.[280] Recent reports have revealed that the pathogen has been isolated from raw beef, pork, and chicken, of which the rate of isolation from chicken was greater compared to others. The prevalence of *A. butzleri* on broiler carcasses suggests its presence in poultry abattoirs, and that contamination could be processing associated.[283] In addition, *A. butzleri* has been isolated from several water sources, including groundwater, seawater, bays, surface water, and raw sewage.[275] More importantly, the pathogen has been isolated from well water, water treatment plants, and other sources of water storage.[276] It has also been observed that *A. butzleri* can attach to stainless steel, copper, and plastic pipelines[276] that carry water indicating its adherence potential on abiotic surfaces.

Little information is known regarding the virulence mechanisms by which *A. butzleri* infects humans and animals. However, it has been determined that *A. butzleri* is highly adherent, invasive, and cytotoxic to cell cultures. *A. butzleri* is the most invasive species among the arcobacters[284] based on its ability to colonize piglet intestines, although variable results on colonization of chicken and turkeys were observed.

Brucella Species

Brucella spp. are pathogens in many animals, causing sterility and abortion. In humans, *Brucella* is the etiologic agent of undulant fever. The genus *Brucella* consists of six species, of which those of principal concern are *B. abortus*, *B. suis*, and *B. melitensis*.[285] *B. abortus* causes disease in cattle and *B. suis* in swine, and *B. melitensis* is the primary pathogen of sheep. *B. melitensis* is the most pathogenic species for humans. Human brucellosis is primarily an occupational disease of veterinarians and meat industry workers. Brucellosis can be transmitted by aerosols and dust. Foodborne brucellosis can be transmitted to humans by consumption of meat and milk products from infected farm animals. The most common food vehicle of brucellosis for humans is unpasteurized milk.[285] Meat is a less common source of foodborne brucellosis because the organisms are destroyed by cooking. Since the National Brucellosis Education program has almost eradicated *B. abortus* infection from U.S. cattle herds, the risk of foodborne infection of brucellosis through consumption of domestically produced milk and dairy products is minimal.[103]

Helicobacter pylori

H. pylori is a human pathogen causing chronic gastritis, gastric ulcer, and gastric carcinoma.[286,287] Once colonized in humans, the pathogen could be the predominant species present in the stomach. The infection is mostly acquired early in life (<10 years of age).[288] Although humans are the primary host of *H. pylori*, the bacterium has been isolated from cats.[212] *H. pylori* does not survive well outside its host, but it has been detected in water and vegetables.[289,290] A study on the effect of environmental and substrate factors on the growth of *H. pylori* indicated that the pathogen likely lacks the ability to grow in most foods.[291] However, *H. pylori* may survive for long periods in low-acid environments under refrigerated conditions. *H. pylori* infections spread primarily by person-to-person transmission, especially among children, and contaminated water and food are considered potential vehicles of the pathogen. In the United States, a significant

association between *H. pylori* infection and iron-deficiency anemia, regardless of the presence or absence of peptic ulcer, has been reported.[292,293]

Viral Foodborne Pathogens

Estimates by the CDC of the incidence of foodborne illness in the United States indicate that viruses are responsible for approximately 67% of the total foodborne illnesses of known etiology annually (Table 3.2).[204] Viruses are obligate intracellular microorganisms and most foodborne viruses contain RNA rather than DNA. Since viruses are intracellular organisms requiring a host for multiplication, they cannot grow in foods. Therefore, the number of virus particles on foods will not increase during processing, transport, or storage, causing no deterioration in food quality.[294] Foodborne viruses are generally enteric in nature, causing illness through ingestion of foods and water contaminated with human feces (fecal–oral route). Viruses disseminated through foods also can be spread by person-to-person contact. For example, research with hepatitis A virus has revealed that a few hundred virus particles can readily be transferred from fecally contaminated fingers to foods and surfaces.[295] Fresh produce and shellfish are generally common sources of viral contamination and thus considered as high-risk foods.[296] Hepatitis A virus, norovirus (previously known as Norwalk-like viruses), and possibly rotavirus are among the most significant of the viruses that are foodborne.

Hepatitis A Virus

Hepatitis A virus is a member of the family *Picornaviridae* and is transmitted by the fecal–oral route. Raw shellfish harvested from waters contaminated by human sewage is among the foods most frequently associated with outbreaks of hepatitis A virus.[297] Besides shellfish, other foods including sandwiches, dairy products, baked products, salads, fruits, and vegetables have also been implicated in various outbreaks of hepatitis A virus.[298,299] A large outbreak in Pennsylvania in 2003 involving more than 500 cases was linked to ingestion of contaminated green onions.[300] Hepatitis A virus is more resistant to heat and drying than other picornaviruses.[297] The incubation period for onset of symptoms of hepatitis A infection ranges from 15 to 45 days, and symptoms include nausea, abdominal pain, jaundice, and fever. The virus is shed in feces by infected humans many days before the onset of symptoms, indicating the importance of good personal hygienic practices of cooks and food handlers who could otherwise contaminate food during the period of asymptomatic fecal shedding. The overall incidence of hepatitis A virus in the United States has decreased since the implementation of routine childhood vaccination against the virus in 1996.[104] In 2007, the CDC reported that the incidence of hepatitis A infections was at their lowest level.[301]

Norovirus

Norovirus belongs to the family *Caliciviridae* and is often referred to as small, round-structured viruses. Norovirus is recognized as the most common viral cause of foodborne and waterborne acute gastroenteritis in the United States.[1] The virus possesses a low infectious doze of less than 100 virus particles.[302] Raw or undercooked shellfish and other seafoods are common vehicles of norovirus. The incubation period of infection ranges from 24 to 48 h, and symptoms include nausea, vomiting, and diarrhea. The young, immunocompromised, and elderly are considered to be at greatest risk of developing severe illness caused by the pathogen.[303] Infected humans shed the virus in feces for up to a week after symptoms have subsided. The virus survives freezing, heating to 60°C, and chlorine levels up to 10 ppm.[302] Qualitative studies in human volunteers indicate that the viruses are infective for up to 3 h when exposed to a medium at pH 2.2 at room temperature or for 60 min at pH 7 at 60°C.[304]

The impact of norovirus on the U.S. economy is large. A recent study revealed that the virus causes an estimated 5 million cases, resulting in 14,663 hospitalizations and 149 deaths, which accounts for a loss of $2.8 billion.[3] In 2009, the United States launched CaliciNet, an outbreak surveillance network for noroviruses. Of 558 norovirus outbreaks submitted to the CaliciNet since 2009, 14% were associated with foodborne transmission. Of the five genogroups (GI–GV), GI and GII were the most common affecting humans. The genogroup GII has 19 genotypes, of which GII.4 caused more than 85% of the norovirus outbreaks. A GII.4 variant called GII.4 New Orleans emerged as the major disease-causing genotype in October 2009, replacing another variant, GII.4 Minerva, that was the common outbreak strain since 2005.[305]

Rotavirus

Rotavirus is a nonenveloped, double-shelled virus, with a genome comprised of 11 segments of double-stranded RNA. It is characterized by two surface-expressed neutralizing antigens, a glycosylated outer surface protein (G protein) encoded by the VP7 gene and a protease-cleaved protein (P protein) encoded by the VP4 gene. Rotavirus is the most common cause of diarrhea in children worldwide, especially in developing countries. In the United States and other countries with a temperate climate, infection with rotavirus has been reported to peak during the winter season (November to April). In the United States, there are an estimated 3.9 million cases of rotavirus diarrhea each year; however, only 39,000 cases are estimated to be acquired through contaminated foods.[204] Rotavirus infection has an incubation period of 1–3 days and is characterized by fever, vomiting, and diarrhea. The virus is shed in the feces of infected humans and can survive on vegetables at 4°C or 20°C for many days.[306] It has also been shown to survive the process of making soft cheese.[306] The primary mode of transmission of rotavirus is by fecal-to-oral route. In early 2006, the U.S. Food and Drug Administration approved a new live, oral vaccine (RotaTeq™) for the prevention of rotavirus gastroenteritis in infants. This pentavalent vaccine expresses five different genotypes of the virus, namely, G1, G2, G3, G4, and, the most common P-type, P1A. During the surveillance periods 2005–2006 and 2006–2007, G1 was predominant, and

TABLE 3.2
Viral Foodborne Pathogens

Microorganism	Significant Characteristics	Sources/ Reservoirs	Examples of Vehicles	Estimated No. of Foodborne Cases Annually in the United States[2,3]	Incubation Period, Symptoms, and Duration	Detection Methods	Control/Prevention
Hepatitis A virus	Single-stranded RNA virus, spherical in shape, remains viable for long periods of time in foods stored at refrigeration temperature; virus multiplies in the gut epithelium before being carried by blood to the liver. Virus is shed in feces before symptoms of liver damage become apparent.	Humans, sewage-polluted waters	Raw or undercooked shellfish and seafoods harvested from sewage-polluted water, ready-to-eat foods such as salads prepared by infected food handler	1,566	15–45 days, usually ca. 25 days. Loss of appetite, nausea, abdominal pain, fever, jaundice, dark urine, pale stools. Duration is a few weeks to months.	Cultural methods[592,593] Enzyme immunoassay[594] PCR[595–598] LAMP assay[599] Immunochromatography assay[600]	Avoid consumption of raw seafoods; disinfection of drinking water, good personal hygiene and food handling practices, vaccination of professional food handlers, safe sewage disposal
Norovirus	Single-stranded RNA virus, spherical in shape, does not multiply in any known laboratory host.	Humans, sewage-polluted waters	Raw or undercooked shellfish and seafoods harvested from sewage-polluted water, drinking water	5,461,731	1–2 days. Loss of appetite, nausea, abdominal pain, diarrhea, vomiting, headache. Duration is 2 days.	Enzyme immunoassay[601,602] PCR[603–607] Latex agglutination test[608] Third-generation ELISA coupled with immunochromatography[609] DNA microarray[610]	Avoid consumption of raw seafoods, disinfection of drinking water, good personal hygiene and food handling practices, hygienic sewage disposal, treatment of wastewater used for irrigation
Rotavirus	Double-stranded RNA virus, icosahedral in shape.	Humans	To be determined	15,433	1–3 days. Vomiting, abdominal pain followed by watery diarrhea. Duration is 6–8 days.	Cultural methods[592,593] ELISA[611,612] PCR[612–615] Flow cytometry[310,616] Immunobiosensor[617]	Avoid consumption of raw seafoods Avoid drinking of untreated water Good personal hygiene
Avian influenza virus	Single-stranded RNA virus, medium sized, pleomorphic, enveloped.	Chicken, turkey, guinea fowl, and migratory waterfowl	Raw or undercooked contaminated egg and poultry meat	Emerging disease Not reported in the United States 132 cases worldwide (1997–2005)	Typical flu symptoms such as fever, cough, sore throat, and muscle aches. Also eye infections (conjunctivitis), pneumonia, and acute respiratory distress can be present.	Cultural method[310] Rapid antigen detection test[618] PCR[310,619,620] Serological test[310] Resequencing microarray[621]	Avoid consumption of raw or undercooked poultry meat and egg Avoid using raw eggs for preparing foods that are not cooked Avoid handling and slaughtering of infected birds or birds suspected of infection Use hygienic practices during slaughter and postslaughter operations

during 2007–2008, G3 replaced G1. Currently monitoring of strains for any possible vaccine-pressure-induced changes is underway. Another live attenuated rotavirus vaccine based on genotype G1P, Rotarix, is currently approved for use in the United States.[307]

Avian Influenza Virus

Avian influenza (bird flu) is a highly contagious viral infection affecting a wide species of birds, including chicken, turkey, guinea fowl, and migratory waterfowl. The disease is of tremendous economic significance to the poultry industry. Recent outbreaks of avian influenza infections in poultry and humans highlight the zoonotic potential of the disease and its impact on public health.[308] During the period from 1997 to 2005, 132 human cases of avian influenza with 64 deaths have been reported worldwide.[309] Based on virulence, avian influenza virus can be classified into the highly pathogenic avian influenza (HPAI) strains that cause a systemic lethal infection, resulting in death of birds as early as 24 h to 1 week postinfection, and the low pathogenic avian influenza (LPAI) viruses that rarely result in fatal disease in birds.[284] The HPAI viruses that cause "fowl plague" are restricted to the subtypes H5 and H7; however, all the viruses of these subtypes do not cause HPAI. H5N1 is the influenza A virus subtype that occurs mainly in birds, causing fatal disease in birds.

Avian influenza viruses, belonging to the family Orthomyxoviridae, are medium-sized, pleomorphic, enveloped viruses with glycoprotein projections from the envelope having hemagglutinating (HA) and neuraminidase (NA) activities.[310] The genome of the virus consists of eight segments of single-stranded RNA of a negative sense, which code for ten viral proteins. Antigenically, three distinct types of influenza viruses are reported, namely, type A, type B, and type C, with the former type causing natural infections in birds. Based on the antigenic properties of hemagglutinin and neuraminidase surface glycoproteins, type A influenza viruses are divided into various subtypes.[311] Currently, 15 HA and 9 NA subtypes have been reported.[284] The ability of these viruses to transform by recombination and assortment enables them to adapt to new hosts, including humans.

The hemagglutinin glycoproteins play a vital role in the pathogenicity by mediating attachment of the virus to host cell receptors followed by release of viral RNA.[308] The HA glycoprotein precursor (HA0) is posttranslationally cleaved into HA1 and HA2 subunits by host proteases, with the HA2 amino terminus mediating fusion between the viral envelope and the endosomal membrane.[312] Klenk et al.[313] reported that proteolytic activation of HA glycoprotein is essential for viral infectivity and dissemination, thus highlighting its role in the pathogenesis of avian influenza virus. The HA precursor proteins of LPAI viruses have a single arginine at the cleavage site; hence, these viruses are limited to cleavage by host proteases such as trypsin-like enzymes. Therefore, replication of LPAI viruses is limited to sites (organs) where such enzymes are found (respiratory and intestinal tracts), thereby resulting in mild infections. However, the HAs of HPAI viruses contain multiple basic amino acids at the cleavage site, which are cleaved by ubiquitous proteases present in a variety of host cells. These viruses therefore are able to replicate throughout the bird, causing lethal systemic infection and death.[314,315]

The source of infection to poultry in most outbreaks is direct or indirect contact with waterbirds. Once the infection is established in birds, the disease is highly contagious. Fecal-to-oral transmission is the most common mode of spread between birds. Contact with infected material is the most important mode of transmission from bird to bird. In infected birds, the virus is excreted in the droppings and nasal and ocular discharges. Fecal shedding of the virus by infected birds has been documented up to 4 weeks postinfection. Contaminated feed, water, rodents, and insects can also play a role in the spread of virus. Movement of infected birds, contaminated equipment, egg flats, feed truck, and service crew can also spread the virus from flock to flock. Airborne transmission of the virus can potentially occur if birds are kept in close proximity and with air movement. Since lesions have been reported in the ovaries and oviducts of infected egg-laying chickens, avian influenza virus could potentially be transmitted via the egg either through virus in the internal egg contents or on the surface from virus-infected feces.[316] This could potentially lead to hatching of infected chicks and contamination of the hatchery. Implementation of strict biosecurity measures can greatly reduce the risk of secondary spread after an initial outbreak.

Although humans can contract avian influenza virus by handling and slaughtering of infected birds, there is no epidemiologic evidence to suggest transmission of the virus by consumption of properly cooked eggs or other cooked poultry products derived from infected birds. Cooking poultry meat to 160°F (71°C) inactivates the virus.[309] Consumption of raw or partially cooked eggs (runny yolk) or foods containing raw eggs should be avoided. Avian influenza viruses remain viable in contaminated poultry meat and potentially spread through the marketing and distribution of contaminated fresh or frozen poultry meat.

In addition to birds, swine can serve as a critical animal reservoir for the emergence of new influenza A viruses because swine can be infected by both human and avian influenza viruses. For example, the classical H1N1 swine influenza viruses were very similar to the human pandemic influenza isolates of 1918. Moreover, human-associated H3N2 viruses were isolated from pigs shortly after they were identified as disease-causing agents in humans.[317]

Fungal Foodborne Pathogens

Molds are widely distributed in nature and are an integral part of the microflora of foods. Although molds are major spoilage agents of many foods, many molds also produce mycotoxins of which some are carcinogenic and mutagenic (Table 3.3). Mycotoxins are secondary metabolites produced by molds usually at the end of their exponential phase of growth. Some of the

TABLE 3.3
Fungal Foodborne Pathogens

Microorganism/Toxin	Significant Characteristics	Sources/ Reservoirs of Fungi	Examples of Vehicles of Toxins	Toxic Effects	Detection Methods	Control/ Prevention
A. parasiticus and *A. flavus*/aflatoxin	Growth at 10°C–43°C, optimal growth at 32°C, produces aflatoxins at 12°C–40°C, growth at pH 3–11	Environment, soil, vegetation	Corn, peanuts, cottonseed	Effects of aflatoxin in animals: Acute: hemorrhage in the gastrointestinal tract, liver damage, death Chronic: cirrhosis of liver, liver tumors, immunosuppression	Cultural methods[330,622–624] ELISA[625] Immunoassay[626,627] PCR[628–632] Functionalized-gold nanoparticles[633] Enzyme-linked-immunomagnetic-electrochemical array[634] Near-infrared spectroscopy[635] Monoclonal antibody-based ELISA[636] Electrochemical immunosensor[637] Antibody-based microarray[638]	Proper storage of cereal products, detoxification of mycotoxins in cereal products by treatment with hydrogen peroxide, ammonia
P. expansum/patulin, *P. citrinum*/citrinin	*P. expansum* is psychrotrophic, capable of growth at −2°C – –3°C and optimal growth at 25°C,	Environment, soil, vegetation	*P. expansum*: Fruits, especially apples and pears *P. citrinum*: Cereals, especially rice, wheat, corn	Effects of patulin: Gastrointestinal, neurological immunological effects in animals Citrinin: Fatty degeneration and renal necrosis in pigs and dogs; significance in human health is unresolved	Cultural methods[330,623,639] PCR[640–642] Detection of mycotoxin by HPLC[643,644] mass spectrometry[645] Competitive fluorescence assay[646] ELISA[647]	Avoid consumption of rotten apples and pears, proper storage of cereal products
F. graminearum/ deoxynivalenol, nivalenol, zearalenone	Growth at 5°C but not at 37°C, optimal growth at 25°C	Environment, soil, vegetation	Cereals, especially wheat, barley, corn	Effects of deoxynivalenol: nausea, vomiting, abdominal pain, diarrhea, headache, fever, chills, throat irritation	Cultural methods followed by morphology[648,649] PCR[642,650–654] Immunoassay[655] ELISA[656] LAMP assay[657]	Proper storage of cereal products

principal species of molds, which produce mycotoxins in foods, include the following.

Aspergillus Species

A. flavus and A. parasiticus are the most important toxigenic foodborne aspergilli. A wide variety of foods such as nuts, corn, oil seeds, and sorghum are potential vehicles of these aspergilli. *Aspergillus* species can cause disease in animals and humans by infection (aspergillosis) or by toxin production (aflatoxicosis). *A. flavus* and *A. parasiticus* produce aflatoxins, which are difuranocoumarin derivatives.[318] The common types of aflatoxins that are produced are B_1, B_2, G_1, and G_2.[319] In addition, two other types of aflatoxins, namely, M1 and M2, have also been reported as contaminants in food and feeds. Aflatoxicosis in animals can be acute or chronic. Acute cases are characterized by severe liver damage, whereas liver cirrhosis, liver cancer, and teratogenesis occur in chronic toxicity. Chronic intake of aflatoxins in animals can lead to poor feed conversion and low weight gain. Although fungal toxins cause an estimated economic loss of $1 billion in the United States, most of this is from aflatoxin contamination. The FDA has regulated the concentration of aflatoxin in the milk at not more than 0.5 and 20 ppb in crops.[320] Several outbreaks associated with aflatoxin consumption by humans have been recorded in developing countries.[320–322]

In humans, aflatoxins have been reported to cause hepatic cancer. A significant correlation between aflatoxin exposure and stunted growth has been reported in children exposed to aflatoxin during neonatal stages.[323] Additionally, since aflatoxins can cross the placental barrier, they can potentially lead to genetic defects in the fetus.[324] Following intake, aflatoxins are metabolized into a variety of products such as aflatoxicol, aflatoxin Q1, aflatoxin P1, and aflatoxin M1 in the liver by cytochrome p450 group of enzymes. In addition, another metabolite called aflatoxin 8,9 epoxide can also be formed, which can induce mutations by forming DNA adducts, ultimately leading to hepatic carcinoma.[325–327] Susceptibility of a given species to aflatoxins depends on its liver detoxification systems, genetic makeup, age, and other nutritional factors.[328]

Penicillium Species

The genus *Penicillium* consists of more than 150 species, of which nearly 100 produce known toxins. Three important foodborne toxigenic *Penicillium* species include *P. verrucosum*, *P. expansum*, and *P. citrinum*. *P. verrucosum* is present on grains grown in temperate zones and is commonly associated with Scandinavian barley and wheat.[329] *P. verrucosum* produces ochratoxin A, which has immunosuppressive and potential carcinogenic properties.[329] Ochratoxin A also has been associated with nephritis in pigs in Scandanavia.[330] *Penicillium expansum*, a psychrotrophic mold and one of the most common fruit pathogens, causes a condition known as "blue mold rot" on a variety of fruits, including apples, cherries, nectarines, and peaches.[331–334] Besides its economic impact, *P. expansum* is also of potential public health significance since it produces patulin, a mycotoxin known to cause immunological, neurological, and gastrointestinal toxic effects in animal models.[329] Exposure to high levels of patulin also results in vomiting, salivation, anorexia, polypnea, weight loss, leukocytosis, erythropenia, and necropsy lesions of hemorrhagic enteritis in piglets.[335] Although the toxic effects of patulin in humans have not been proven conclusively, the presence of patulin has been demonstrated in apple juice[336] and grape juice.[337] This is a major concern since fruit juices, especially apple juice, are commonly consumed by infants and children. *P. expansum* is commonly present in rotten apples and pears and to a lesser extent in cereals. Use of moldy fruits contaminated with *P. expansum* greatly increases the risk of patulin contamination in fruit juices. An unusual characteristic of *P. expansum* is its ability to grow at low temperature, i.e., –2°C to –3°C.[329]

P. citrinin is a widely occurring mold commonly present on rice, wheat, and corn. *P. citrinin* produces the metabolite citrinin. Although the toxicological effect of citrinin in humans is not known, it has been reported to cause renal toxicity in pigs and cats.[338]

Fusarium graminearum

F. graminearum is a toxigenic mold commonly present in soil and on cereals such as wheat and corn. It causes "head blight" of wheat and barley and "stalk and cob rot" of maize. The head blight condition resulted in an estimated $1 billion loss in 1993 alone and affected cereal farming in the United States significantly.[339] It produces a number of mycotoxins, including deoxynivalenol and zearalenone.[340] Cereals containing high levels of deoxynivalenol are unacceptable for human or animal consumption. Ingestion of foods containing deoxynivalenol produces illness termed scabby grain intoxication, which is characterized by anorexia, nausea, vomiting, diarrhea, dizziness, and convulsions. Foods most frequently implicated as vehicles of deoxynivalenol include cereal grains, wheat, barley, and noodles. Zearalenone, the other *Fusarium* toxin, is an estrogenic compound that causes sterility in animals.[341]

Parasitic Foodborne Pathogens

Parasitic diseases account for 3% of foodborne illnesses and 21% of foodborne illness-related deaths in the United States (Table 3.4).[204] However, the actual number of parasitic diseases could be higher since they are often underdiagnosed and underreported in the United States.[341] Parasites constitute more of a food safety concern now than in the past because of the globalization of our food supply with growing imports of fruits, vegetables, and ethnic foods from countries, where the hygienic and quality control standards in food production may be suboptimal. Foods can be vehicles of several types of parasites, including protozoa, roundworms, and flatworms. Although foodborne transmission of parasites such as *Trichinella spiralis* and *Taenia solium* has been known for many years, the foodborne disease potential of many protozoan parasites such as *Cryptosporidium* and *Cyclospora* has only recently been recognized.

TABLE 3.4
Parasitic Foodborne Pathogens

Parasite	Significant Characteristics	Sources/ Reservoirs	Vehicles	Estimated No. of Foodborne Cases Annually in the United States[2,3]	Incubation Period, Symptoms, and Duration	Detection Methods	Control/Prevention
G. lamblia	Flagellate protozoa, produces oval-shaped cysts ranging from 8 to 20 µm in length and 5–12 µm in width; cysts contain four nuclei and are resistant to chlorination used to disinfect water	Humans, animals, especially beavers and muskrats, water	Drinking water, raw fruits and vegetables contaminated with cysts, ready-to-eat foods such as salads contaminated by infected food handlers	76,840	4–25 days, usually 7–10 days Abdominal cramps, nausea, abdominal distension, diarrhea that can be chronic and relapsing, fatigue, weight loss, anorexia Duration is weeks to years	Immuno-fluorescence[658] Immunochromatography[659,660] PCR[661–665] ELISA[666] Surface-enhanced resonance spectroscopy[667] Biosensors[668] Flow cytometry[669]	Adequate cooking of foods, filtration of drinking water, good personal hygiene and food handling practices
E. histolytica	Amoeboid protozoa, anaerobe survives in environment in crypted form, cysts remain viable in feces for several days and in soil for at least 8 days at 30°C and for more than 1 month at 10°C, relatively resistant to chlorine	Humans, dogs, rats	Foods and water contaminated with feces or irrigation water	Unknown	2–4 weeks Abdominal pain, fever, vomiting, diarrhea containing blood and mucus, weight loss Duration is weeks to months	Microscopic examination Line dot hybridization assay[670] ELISA[671,672] PCR[663,673,674] LAMP assay[675]	Good personal hygiene and food handling practices, adequate cooking of foods, filtration of water, hygienic disposal of sewage water, treatment of irrigation water
C. parvum	Obligate intracellular coccidian parasite; oocysts are spherical to oval in shape with an average size of 4.5–5.0 µm; oocysts are resistant to chlorination used to disinfect water	Humans, wild and domestic animals, especially calves	Contaminated drinking and recreational water, raw milk from infected cattle, fresh vegetables and other foods contaminated with feces from infected humans and animals	57,616	2–14 days Profuse, watery diarrhea, abdominal pain, nausea, vomiting Duration is few days to 3 weeks	Immunofluorescence assay[676] PCR[673,677–680] Rapid assay[681] Monoclonal antibody-based dot blot assay[682] Electrochemical-based enzyme-linked biosensor[683] Surface-enhanced resonance spectroscopy[667] Piezoelectric-excited millimeter-sized cantilever sensor[684]	Thorough cooking of food, avoid contact with infected animals, filtration of drinking water, good personal hygiene and food handling practices

(*continued*)

TABLE 3.4 (continued)
Parasitic Foodborne Pathogens

Parasite	Significant Characteristics	Sources/ Reservoirs	Vehicles	Estimated No. of Foodborne Cases Annually in the United States[2,3]	Incubation Period, Symptoms, and Duration	Detection Methods	Control/Prevention
C. cayetanensis	Obligate intracellular coccidian parasite; oocysts are spherical in shape with an average size of 8–10 µm	Humans	Water, fruits, and vegetables contaminated with oocysts	11,407	1 week Watery diarrhea, abdominal pain, nausea, vomiting, anorexia, myalgia, weight loss Duration is a few days to 1 month	Staining and microscopic examination[671] Flow cytometry[685] PCR[686–689]	Good personal hygiene, filtration of drinking water
T. gondii	Obligate intracellular coccidian protozoa	Cats, farm animals, transplacental transmission from infected mother to fetus	Raw or undercooked meat, raw goat milk, raw vegetables	86,686	5–23 days Fever, rash, headache, muscle pain, swelling of lymph nodes; transplacental infection may cause abortion Duration is variable	Cell culture and mouse inoculation[690] Immunoassay[691] Serological assay[692] Immunofluorescence[693] PCR[694–698] LAMP assay[699] Oligonucleotide microarray[700]	Prevent environmental contamination with cat feces, avoid consumption of raw meat and milk, safe disposal of cat feces, wash hands after contact with cats
T. spiralis	Nematode with no free-living stage in the life cycle; adult female worms are 3–4 mm in length; transmissible form is larval cyst, which can occur in pork muscle	Wild and domestic animals, especially swine and horses	Raw or undercooked meat of animals containing encysted larvae such as swine or horses	156	Initial symptoms: 24–72 h Systemic symptoms: 8–21 days Initial phase: Abdominal pain, fever, nausea, vomiting, diarrhea Systemic phase: Periorbital edema, eosinophilia, myalgia, difficulty in breathing, thirst, profuse sweating, chills, weakness, prostration Duration is 2 weeks to 3 months	Microscopic examination ELISA[701,702] Immunoassay[703] PCR[704–707]	Adequate cooking of meat, freezing of meat at −15°C for 30 days or at −35°C, preventing trichinosis in pigs by not feeding swine garbage containing infected meat

Anisakis spp.	Nematode, slender threadlike parasite measuring 1.5–1.6 cm in length and 0.1 cm in diameter	Sea mammals	Some undercooked salt water fish, sushi, herring, sashimi, ceviche	Unknown	4–12 h Epigastric pain, nausea, vomiting, sometimes hematemesis Duration is variable	ELISA[708,709] Immunoblot[710] PCR[711–714] Fluorescence PCR[715]	Adequate cooking of saltwater fish, freezing fish at −23°C for 7 days
T. solium *T. saginata*	Tapeworm, dependent on the digestive system of the host for nutrition	Humans, cattle, swine	Raw or undercooked beef or pork	Unknown	Few days to >10 years Nausea, epigastric pain, nervousness, insomnia, anorexia, weight loss, digestive disturbances, weakness, dizziness Duration is weeks to months	Detection of eggs or proglottids in feces ELISA[716,717] PCR[718–720]	Adequate cooking of beef and pork, proper disposal of sewage and human wastes, freezing of meat at −10°C for 2 weeks
D. latum	Largest human tapeworm	Saltwater fish, humans	Raw or undercooked saltwater fish	Unknown	Epigastric pain, nausea, abdominal pain, diarrhea, weakness, pernicious anemia Duration is months to years	Detection of eggs in feces	Adequate cooking of fish, proper disposal of sewage and human waste

Unlike bacteria, parasites do not multiply in foods. Moreover, parasites need at least one specific host to complete their life cycle. Many of the well-recognized parasites that can be transmitted to humans through foods include the following.

Giardia lamblia

Giardiasis is the most common parasitic infection reported in the United States, with 21,300 confirmed cases in 1997.[342] However, the numbers have significantly increased over 15 years. A recent study revealed 76,840 cases of *Giardia lamblia* infections causing 225 hospitalizations.[3] *G. lamblia* is a flagellated protozoan parasite that colonizes the intestinal tract of humans and animals. It is commonly present in lakes, rivers, and stagnated waters. The parasite has a very low infective dose, with about 25–100 cysts for causing infection.[343] The life cycle of *G. lamblia* includes flagellated trophozoites, which become pear-shaped cysts.[344] The cysts contaminate water or food through feces of infected animals or humans. Following ingestion of cyst-contaminated water or food, the trophozoites reach the small intestine where they undergo excystation and multiply by binary fission. New trophozoites subsequently become cysts in the distal small intestine, and the encysted trophozoites are shed in the feces. The symptoms of giardiasis include abdominal pain, abdominal distension, nausea, vomiting, and diarrhea. Although water and foods contaminated with cysts are primary vehicles of giardiasis, little is known about the survival characteristics of the cysts in foods. In most cases of foodborne transmission, infected food handlers transfer the cysts to foods they prepare. Humans can also contract giardiasis through the use of contaminated water for irrigating or washing fruits and vegetables.[345] Contaminated water was identified as the source of *Giardia* oocysts in several outbreaks of giardiasis from 1954–2001.[346]

Entamoeba histolytica

E. histolytica is a protozoan parasite that causes amoebiasis or amoebic dysentery in humans. Although the parasite survives in the environment and water, humans are the principal source of amoebiasis. In humans, cysts containing the trophozoites are released, which in turn multiply, and are subsequently excreted in the feces as cysts.[278] Foods and water contaminated with the cysts transmit the disease. Since the fecal–oral route is the principal route of transmission of amoebiasis, personal hygiene of infected food handlers plays a critical role in preventing foodborne amoebiasis. Human amoebiasis can occur in two forms: intestinal amoebiasis and amoebic liver abscess, which is usually a sequel to the intestinal form. Intestinal amoebiasis is characterized by abdominal pain, vomiting, and watery diarrhea containing mucus and blood. Symptoms of the hepatic form of amoebiasis include wasting, painful and enlarged liver, weight loss, and anemia. Amoebiasis is a common cause of diarrhea in tropical and subtropical countries, and most cases in the United States are reported in immigrants and persons returning from endemic areas.[345]

Cryptosporidium parvum

C. parvum is a protozoan parasite that infects a wide range of animals and humans. *C. parvum* is monoxenous in its life cycle, requiring only one host for its development.[344] Infected hosts shed in their feces oocysts of the parasite, subsequently contaminating the environment, food, and water. The life cycle of *C. parvum* can be summarized as follows.[344] Upon ingestion of contaminated water or food, or by inhalation of oocysts, sporozoites are released by excystation of oocysts into the gastrointestinal or respiratory tract. The sporozoites enter the epithelial cells and develop into trophozoites, which in turn differentiate into type I and type II meronts. The merozoites from type I meronts invade new tissues and develop into trophozoites to continue the life cycle. The merozoites from type II meronts invade infected cells and undergo sexual multiplication to give rise to male and female gametes. The zygotes resulting from fertilized gametes become infectious by sporulation, and the sporulated oocysts are excreted in feces. *C. parvum* has an infectious dose of about 9–1042 oocysts.[343]

Cryptosporidiosis is a self-limiting disease with an incubation period of 1–2 weeks and is characterized by profuse, watery diarrhea, abdominal pain, vomiting, and low-grade fever. During the period from 1993 to 1998, seven major outbreaks of cryptosporidiosis have been reported in the United States.[345] Since then, *Cryptosporidium* spp. caused an estimated 57,600 illnesses, 210 hospitalizations, and 4 deaths.[3] Water is the most common source of *C. parvum* for human infections.[212] The largest outbreak of cryptosporidiosis (waterborne) in the United States occurred in Milwaukee, Wisconsin, in 1993 involving more than 400,000 people with 69 deaths.[347,348] In addition to drinking water, water can also potentially contaminate produce when it is used for irrigating plants or washing fruits and vegetables. Oocysts of the pathogen have been detected in fresh vegetables, raw milk, sausage, mussels, oysters, and apple cider.[212] Infected food handlers can also transfer the oocysts to foods.[349,350] *C. parvum* oocysts are sensitive to freezing and freeze-drying. The oocysts lose infectivity in distilled water stored at 4°C.[351] However, the oocysts are quite resistant to chlorine; no loss in infectivity was observed in water containing 1%–3% chlorine for up to 18 h.[352] However, the oocysts are sensitive to ozone, losing more than 90% infectivity in the presence of 1 ppm ozone for 5 min.[353]

Besides affecting humans, *C. parvum* can infect cattle, preweaned calves, sheep and goats, pigs, and horses.[354] *C. parvum* oocysts were responsible for an outbreak of cryptosporidiosis in veterinary students involved in research with cattle,[355] underscoring the pathogen's zoonotic potential.

Cyclospora cayetanensis

C. cayetanensis is a waterborne protozoan pathogen that is also transmitted by contaminated food. The parasite was implicated in several foodborne outbreaks in the United States during 1996 and 1997.[356] The pathogen causes an estimated 11,400 cases, with 11 hospitalizations annually, costing approximately $11 million.[3] Water and foods,

especially fruits and vegetables containing oocysts, are common vehicles of human infection.[345,357] During the period from 1996 to 2000, eight major outbreaks of cyclosporidiosis were reported, with imported raspberries as the vehicle of infection in half of the outbreaks.[345] Other types of produce implicated in *C. cayetanensis* outbreaks include lettuce[358] and fresh basil.[359] Humans are the only identified reservoir of *C. cayetanensis*.[357] The symptoms of *C. cayetanensis* infection in humans include watery diarrhea, nausea, abdominal pain, vomiting, and weight loss. Presently, there is very little information on the effects of heat, freezing, and disinfection agents on *Cyclospora* oocysts. Exposure of oocysts to –20°C for 24 h or 60°C for 1 h prevented oocysts from sporulating. Exposing oocysts to 4°C or 37°C for 14 days delayed sporulation.[360]

Toxoplasma gondii

T. gondii is an obligate intracellular protozoan parasite for which cats are the definitive host. A survey on the prevalence of *T. gondii* in cats at spay or neuter clinics in Ohio revealed that 48% of the cats were infected with the parasite.[361] In the intestine of cats, the parasite undergoes sexual reproduction to form oocysts, which are excreted in feces.[362] The oocysts undergo maturation and survive in the environment for months and spread by wind, insects, and tapeworms. Toxoplasmosis in humans results following ingestion of food or water contaminated with oocysts. Raw or undercooked meats contaminated with cysts are potential sources of *T. gondii*. The parasite has been isolated from meat of game, sheep, goats, horses, chickens, and swine.[344,363] Transmission also occurs from an infected pregnant mother to child by transplacental transmission.[364] In the United States, *T. gondii* has been reported to cause about 4000 congenital infections annually, potentially resulting in blindness, learning disabilities, and mental retardation in children.[341] *T. gondii* is also attributed as the leading cause of CNS infection in persons with AIDS.[365] Symptoms in healthy adults are usually mild and include rash, headache, muscle pain, and swelling of lymph nodes. Although the oocysts can survive in refrigerated meat for weeks, they are inactivated by freezing at <12°C.[366] The oocysts are sensitive to irradiation and heat (>67°C). Properly cooked foods are not a vehicle of *T. gondii*.[367] *T. gondii* causes an estimated 86,700 cases, 4,428 hospitalizations, and 327 deaths annually, costing an estimated $3 billion, second only to nontyphoidal salmonellosis.[3]

Trichinella spiralis

T. spiralis is a roundworm that primarily infects wild and domestic animals, especially pigs. Humans contract trichinosis by consumption of raw or undercooked meat containing larvae of the parasite. Pigs are infected by consuming uncooked scraps of infected pork. The encysted larvae upon ingestion are liberated from the cyst in the intestine, where they sexually mature.[368] The mature male and female worms copulate in the lumen of the small intestine, giving rise to a new generation of larvae. The newly born larvae migrate to various tissues in the body. Those larvae that reach the striated muscles penetrate into the sarcolemma of the muscle fibers and develop to maturity as encapsulated cysts.[368] The larvae continue their life cycle when raw or undercooked meat, especially pork containing the larvae, is consumed by humans. Major clinical systems include myalgia, diarrhea, fever, facial edema, conjunctival hemorrhages, and headache.[369]

Trichinosis is a notifiable disease in the United States, with the number of cases progressively decreasing since the 1940s.[345] The decline in trichinosis in the United States has been attributed to changes in swine feeding practices and routine inspections at slaughterhouses. The average number of trichinosis cases reported in the United States in 1997–2001 was 14 per year, down from 400 cases/year in the 1940s.[370] On the other hand, game meat was identified as the most common source of the parasite to humans during 1997–2001.[345] Globally, *Trichinella* spp. cause an estimated 65,818 cases and 42 deaths reported from 41 countries during 1986–2009.[369]

Anisakis Species

Anisakiasis in humans is caused by two foodborne roundworms. These include *A. simplex*, whose definitive host is whales, and *Pseudoterranova decipiens*, which primarily inhabits seals. The eggs of these roundworms are excreted in feces by their respective hosts. The eggs then undergo molting in suitable intermediate hosts and subsequently develop into larvae, which are ingested by fish.[371] Humans contract anisakiasis by consumption of raw or undercooked fish and seafoods containing the larvae. In noninvasive anisakiasis, the worms released from ingested foods migrate to the pharynx, resulting in "tingling throat syndrome."[371] The worms are ultimately expelled by coughing. In the invasive form of anisakiasis, the worms penetrate the intestinal mucosa, thereby causing symptoms that include epigastric pain, nausea, vomiting, and diarrhea.

Taenia Species

The genus *Taenia* includes two meatborne pathogenic flatworms, *T. saginata* (beef tapeworm) and *T. solium* (pork tapeworm). The eggs of *T. saginata* survive in the environment, including on pastures, and are ingested by cattle in which they hatch into embryos.[368] The embryos migrate to skeletal muscles or the heart and develop into larvae known as *Cysticercus bovis*. They become infective to humans in approximately 10 weeks.[343] Humans become infected by consuming raw or undercooked beef containing the larvae. Larvae that are released into the small intestine develop into mature, adult worms. Cattle get infected with contaminated human hands or by drinking contaminated feed or water.[372] The symptoms of *T. saginata* infection in humans include decreased appetite, headache, dizziness, diarrhea, and weight loss.

In the normal life cycle of *T. solium*, pigs serve as the intermediate host. Eggs ingested by pigs develop into embryos in the duodenum, penetrate the intestinal wall, migrate through the blood and the lymphatic system, and finally reach the

skeletal muscles and myocardium, where they develop into larvae known as *Cysticercus cellulosae*. Humans, the definitive host, consuming raw or undercooked pork are infected with the larvae, which develop into adult worms in the small intestine. The symptoms of *T. solium* infection in humans include discomfort, hunger pains, anorexia, and nervous disorders. Worms are passed in the feces. In the abnormal life cycle of *T. solium*, humans serve as intermediate hosts in which the larvae develop in striated muscles and in subcutaneous tissue. *T. solium* infections are most common in the developing world. However, due to immigration of people from endemic areas, infections have been increasingly diagnosed and reported in developed countries.[373]

Diphyllobothrium latum

D. latum is commonly referred to as the broad tapeworm because it is the largest human tapeworm.[371] Humans contract diphyllobothriasis by consuming raw or undercooked fish containing the larval forms called plerocercoids. Upon ingestion, the larvae develop into mature worms in the intestines. Eggs produced by mature worms are excreted in feces. If feces containing the eggs contaminate water, the eggs develop into free-swimming larvae called coricidia. Coricidia are ingested by crustaceans, where they develop into a juvenile stage known as procercoid. Following ingestion of infected crustaceans by fish, procercoids develop into plerocercoids to continue the life cycle. Diphyllobothriasis in humans is characterized by nausea, abdominal pain, diarrhea, weakness, and pernicious anemia.[371] Cases of diphyllobothriasis have been associated with eating foods containing raw salmon such as sushi.

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