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BACTERIAL INFECTIOUS DIARRHEA AND THE IMPORTANCE OF GENOME SEQUENCING IN FOOD SAFETY: LITERATURE REVIEW

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ABSTRACT

Many kinds of bacteria cause gastroenteritis and typically manifests with symptoms of vomiting, diarrhea, and abdominal discomfort. These symptoms can vary and range from mild to severe. In some types of gastroenteritis, symptoms come on quickly, but in others, they don't appear for 24 to 48 hours. It is usually self-limited, but improper management of an acute infection can lead to a protracted course. Identification of an etiological agent by bacterial stool culture is required for the management of patients with severe or prolonged diarrhea, symptoms consistent with invasive disease, or a history that may predict a complicated course of disease. Importantly, characterization of bacterial enteropathogens from stool cultures in clinical laboratories is one of the primary means by which public health officials identify and track outbreaks of bacterial gastroenteritis. The prevalence of each pathogen varies with geographical region and population factors. The focus of this review, are responsible for 10–55% of diarrheal episodes, with highest rates occurring in the developing world. However, with increase in international travel and globalization of the food industry, we must be alert to pathogens that which is more typical of the developing world. Increasing antibiotic resistance must also be considered when choosing empirical treatment. Advances in molecular and rapid detection of enteric pathogens hold promise of improved therapeutic, preventative and control strategies.

KEYWORDS: Bacterial diarrhea, genome sequencing, Food Safety.

INTRODUCTION

Approximately 2.2 million deaths caused by diarrheal disease are recorded annually worldwide and most of these cases are attributed to contaminated food and water.[1] Although the vast majority of cases are mild, a significant number of cases are fatal and a high incidence of acute infections and chronic sequel can lead to billions of dollars in medical costs, loss of productivity[2] and frequent recalls.[3] The importance of food safety is not only a problem in developing countries, but also in developed countries, which have advanced food chain monitoring systems.[4] Food-borne diseases continue to be a matter of major concern worldwide despite important developments in safety to reducing the incidence of certain pathogens in foods through better farm practices and food regulations.[5] In the United States food-borne diseases have been estimated to cause 76 million illnesses, 323,000 hospitalizations, and over 5,000 deaths annually.[6] The food production can be very complex with various stages which may allow routes of exposure, meaning that pathogen control is critical in the "farm to fork" food production continuum.[7] In developing countries, a significant proportion of the annual budget of both governments and development partners is spent confronting food-borne diseases, food safety must be recognized and addressed. Minimizing the consumption of unsafe food, may help to ensure the good health of the population and may play a vital role in the economic progress of developing countries. Diarrhea is the most common illness experienced by international travelers in developing tropical and semitropical regions.[8] The outbreak of the lethal strain of *Escherichia coli* in Europe in 2011 highlighted the limits of our present understanding of the evolutionary trends of new pathogens[9] This guideline provides bacterial infectious disease and technical information on enteropathogens most commonly encountered in clinical practice; however, there are many additional bacteria that have been associated with gastroenteritis. Limited information is available for the majority of these and they are reviewed elsewhere. Several of these agents have clinical importance and high enough frequency to mention here (Table 1).

BACTERIAL PATHOGENS

Aeromonas species: over 26 different species of *Aeromonas* have been described as a cause to date, but the vast majority of these are of limited clinical or public health significance. *Aeromonas* spp. are ubiquitous in aquatic habitats and concentrations peak when water temperatures rise substantially during the summer months. Consumable products such as poultry, lamb,

veal, pork and ground beef can harbor Aeromonas spp. Consumption of contaminated foods or potable water or accidental ingestion of untreated water during recreation are the most common sources of infection. In humans, Aeromonas spp. are not considered to be normal gastrointestinal flora and the estimated human intestinal carrier/colonization rate is extremely low in healthy persons.

Most authoritative documents list *Aeromonas spp*. as accepted enteropathogens, although there still are no bona fide outbreaks of gastroenteritis attributable to this genus.[11,12] The incidence of Aeromonas-associated gastroenteritis on a global basis varies dramatically in association with geographic and socioeconomic factors. In developing countries where sanitary conditions are substandard, the reported incidence of Aeromonas diarrhea can be high, ranging from approximately 4% to 22%.[13–16] In industrialized countries, regardless of patient population and sample size, Aeromonas-associated gastroenteritis has been reported at frequencies of 0% to 10%.[17,18]

Aeromonas diarrhea presents as either an acute watery diarrhea (enteritis) or as a more invasive bloody form resembling dysentery or enterocolitis.[17] The secretory form is much more common than the dysenteric variety. A third, extremely rare variation of Aeromonas gastroenteritis presents as a cholera-like illness with profound watery diarrhea. Most intestinal infections associated with *Aeromonas spp*. are self-limiting, although chronic diarrhea exceeding for 1 year has been described.[19,20]

Several potential serious complications can result secondary to Aeromonas gastroenteritis, including ulcerative colitis, pan colitis, segmental colitis, or inflammatory bowel disease.[17] In a few instances, cases of hemolytic-uremic syndrome (HUS) associated with Aeromonas hydrophila or Aeromonas veronii biovar sobria have been reported in infants and adults[21] Some *Aeromonas spp*. have been shown to carry the Shiga toxin (Stx) genes 1 and 2[22] and development of (HUS) in patients infected with *Aeromonas spp*. may be attributable to this virulence factor. The most serious complication of Aeromonas gastroenteritis is translocation from the gut into the circulatory system, producing frank septicemia.[23] This situation typically exists in persons with underlying conditions, including hepatic cirrhosis or malignancies of the circulatory systems. Attributable fatality rates due to *Aeromonas* sepsis range from 32% to 45%.[17]

Bacillus cereus: *B. cereus* is ubiquitous in the environment, being found in decaying organic matter, soil, freshwater and salt water, vegetables and the intestinal tracts of invertebrates.[24] The spores are hydrophobic in nature, resistant to heat, freezing and drying and can survive after gamma radiation and pasteurization processes.[25,26,27] *B. cereus* spores can germinate in foods that are not promptly cooled and refrigerated after meals or in food heated for prolonged periods at temperatures below 60°C. Outbreak surveillance data from 2009 and 2010 documented 427 illnesses associated with 25 outbreaks in the United States due to B. cereus.[28]

There are two distinct syndromes associated with Bacillus cereus food poisoning: an emetic syndrome and a diarrheal syndrome. The emetic syndrome is due to intoxication by a preformed toxin ingested in food. The emetic toxin, called cereulide, it is a plasmid-encoded peptide that is resistant to heat, proteolysis and acid. As such, the toxin is not destroyed by gastric acids or proteolytic enzymes in the intestinal tract or by food reheating.[29] Cereulide is responsible for symptoms of nausea and which appear within 1/2 to 6 h after ingestion vomiting.[25,29,30] These symptoms are similar to those seen with *Staphylococcus aureus* enterotoxins. Symptoms usually resolve within 6 to 24 h, but rare case reports have documented fulminant hepatic failure and death associated with emetic *B. cereus*.[31–34] The emetic toxin is most often found in starchy foods, such as fried rice, pastry and noodles.[35]

The diarrheal syndrome is characterized by abdominal cramps, pain and watery diarrhea within 8 to 16 h of ingestion of food that contains viable vegetative cells or spores of *B. cereus*. The symptoms of this diarrheal illness are similar to those seen with *Clostridium perfringens* food poisoning, Symptoms typically resolve with 12 to 24 h.[35] Although rare, fatalities have occurred with *B. cereus* diarrheal disease.[29] In the diarrhea syndrome, the three pore-forming enterotoxins are expressed by the vegetative cells in the small intestine, which damage the ileal epithelial cell membranes. The 3 enterotoxins are hemolysin BL (HBL), nonhemolytic enterotoxin (NHE) and cytotoxin K.[25,35]

Individuals at increased risk *of B. cereus* diarrheal disease include those with lowered stomach acidity, such as is seen in patients with achlorhydria or the elderly.[36] *B. cereus* has been isolated from the stools of 0 to 43% healthy children and adults, at various concentrations. However, these cases represent transient colonization, most likely obtained from low-level exposure from the environment.[24,37,38]

Campylobacter Species

Campylobacter is one of the leading causes of bacterial diarrhea worldwide.[39] Food Net estimates that 1.3 million persons in the United States are affected each year by Campylobacter infections.[40] The true incidence may be up to 35 times higher due to undiagnosed or unreported cases.[41] Geographic variation in rates of campylobacteriosis has been consistently observed in the United States between 1996 and 2006, with the mean annual rate of culture-confirmed campylobacteriosis being 5-fold higher in California (34 cases per 100,000

population) than in other states.[42] The reason for this difference is unclear, but does not appear to be associated with increased physician visits, laboratory test ordering, or exposure to risk factors among patients in California compared to other states.

Campylobacter inhabits the intestinal tracts of food animals, such as poultry, cattle, swine and sheep and domestic pets, including cats and dogs. The organism rarely causes disease in animals but is shed in the feces. Meat typically becomes contaminated with animal feces harboring *Campylobacter spp*. during slaughtering. Transmission of the organism is typically foodborne, by ingestion of undercooked contaminated meat and meat products or contaminated dairy products. In addition, waterborne infections occur, via consumption of contaminated water and ice. Contact with infected animals, particularly cats and puppies, has also been shown to be a route of transmission. The typical incubation period for Campylobacter is 2 to 5 days, but it may be up to 10 days.[43] Most cases of Campylobacter enteritis are sporadic, but the incidence increases starting in March and throughout the summer months. Outbreaks associated with Campylobacter have been due to consumption of raw milk or well water contaminated with effluent from livestock operations.[44–46] Higher rates of *Campylobacter enteritis* are seen in those <4 years of age and 15 to 44 years of age.[47] Travelers to developing countries are also at increased risk of *Campylobacter enteritis*.

Campylobacter jejuni subsp. jejuni and *Campylobacter coli* are the most common Campylobacter species associated with diarrheal illness. C. jejuni is responsible for >90% of cases.[43,48] *Campylobacter upsaliensis*, which was first isolated from dogs with diarrhea, has also been shown to cause human disease. The incidence of *C. upsaliensis* among patients with diarrhea may be underappreciated, as the organism cannot grow on the selective media typically used to recover Campylobacter in clinical laboratories.[49–51] Other Campylobacter spp. associated with gastroenteritis include *Campylobacter fetus subsp. fetus, Campylobacter lari, Campylobacter concisus, Campylobacter jejuni subsp. doylei* and *Campylobacter hyointestinalis*.[48,52]

C. jejuni and *C. coli* cause indistinguishable infections.[48] Before the onset of diarrhea, a febrile period with malaise, abdominal pain and myalgia occurs in about 50% of symptomatic patients.[43] Diarrhea is characterized by loose watery stools, with or without blood. Blood and fecal white cells may be present. Abdominal cramping can mimic pain associated with acute appendicitis. In most cases, the diarrhea is self-limited, resolving within a week without antimicrobial therapy. However, relapse occurs in 5 to 10% of untreated patients.[43] Extra intestinal Campylobacter infections such as bacteremia, urinary tract infections, cholecystitis, hepatitis, pancreatitis, nephritis, meningitis, abortion and neonatal sepsis have also been reported.[53] Campylobacter bacteremia is typically uncommon, but it occurs more frequently in patients with HIV infection, malignancy and liver disease.[54] Bacteremia and extra intestinal infections are also more common in neonates and the elderly.[55]

Autoimmune complications, such as reactive arthritis and Guillain-Barré syndrome (GBS), can occur post-Campylobacter infection.[56] GBS is an acute paralytic disease of the peripheral nervous system and is seen in approximately 0.1% of Campylobacter cases. Lipooligosaccharides of C. jejuni, which mimic human ganglioside, elicit autoantibodies that then react with peripheral nerve targets.[56] The onset of GBS usually occurs within 2 to 21 days of the diarrheal illness.[59] Reactive arthritis affects 2 to 4% of patients post campylobacteriosis and is characterized by pain and joint swelling that lasts for several weeks to a year.[48] In 5% of cases, arthritis is chronic or relapsing.[57] Symptoms typically begin 3 to 40 days postdiarrhea and most commonly affect the knees.[58]

Clostridium difficile

Clostridium difficile is an obligately anaerobic, spore-forming Gram-positive rod. The spores of C. difficile are resistant to stomach acid, heat and many commercial disinfectants used in hospitals.[60] Following ingestion, exposure of the spores to bile salts in the small intestine triggers germination.[61] Pathogenic strains of *C. difficile* harbor a pathogenicity locus (PaLoc) that encodes the organism's two main virulence factors: toxin A, an enterotoxin (encoded by *tcdA*) and toxin B, a highly potent cytotoxin (encoded by *tcdB*).[62] The individual role of these two toxins in disease are controversial. Clinical isolates of *C. difficile* that do not express toxin A have been isolated from symptomatic patients[63,64], albeit rarely, whereas toxin B-deficient strains have not. Both toxin A- and toxin B-deficient mutants remain capable of causing disease in hamsters, although both are attenuated compared to the wild-type strain.[65]

C. difficile can readily be found in soil, and the intestinal tracts of animals and humans. Colonization rates are as high as 50% in healthy infants and children <1 year of age whereas 3% to 5% of healthy adults are colonized.[66,67] Much higher rates of colonization, 10 to 50%, are seen in high-risk populations, such as hospitalized patients and long-term-care facility residents. Previous antimicrobial use and previous C. difficile infection (CDI) are predictors of colonization in these populations.[68,70] *C. difficile* is acquired through the ingestion of spores via the fecal-oral route or through exposure to spores in the environment. A recent study demonstrated that only a third of CDI cases could be linked by whole-genome sequencing of isolates to a symptomatic patient, whereas the remainder of cases were attributed to exposure from the environment or asymptomatic carriers.[71]

C. difficile is the primary pathogen associated with antibiotic-associated colitis.[72,73] In the United States, the rate of CDI increased 4-fold between 1993 and 2009 but leveled off at 110 per 100,000 hospital stays in 2009.[74] By far the highest rate of CDI is among patients aged 65 and older, with over 1,000 cases per 100,000 hospitalizations in 2009 reported for this age group.[74]

In 2005, the NAP1/027/B1 strain emerged in Canada, Europe and the United States, concomitant with a significant rise in morbidity and mortality associated with CDI over those in previous years.[75,76] At the time, this change in severity of CDI was attributed to the "hypervirulent" nature of the NAP1/027/B1 strain, this strain has since become the predominant strain in many locations and it continues to be associated with high mortality and relapse rates.[77] Early studies pointed to heightened toxin expression[78], more efficient sporulation[79,80], expression of the binary toxin and fluoroquinolone resistance[75] as reasons for the epidemiological success of this strain. However, some studies questioned the relevance of the NAP1/027/B1 strain type in disease severity[81,82] and it has since been confirmed that not all NAP1/027/B1 strains express larger quantities of toxin than historical strains.[83]

The range of symptoms associated with infection with toxigenic *C. difficile* includes asymptomatic carriage, mild to moderate diarrhea and pseudomembranous colitis (PMC). Patients may present with a brief, self-limiting diarrhea or with profuse watery diarrhea similar to that in cholera.[84] Fever, abdominal cramping and leukocytosis can be seen in individuals with more severe diarrhea. Persons with PMC present with abdominal pain, fever, marked leukocytosis and severe diarrhea that may be bloody. Poor prognostic indicators include a rapid increase in the peripheral white blood count with an increase in band forms and a sudden absence of diarrhea.[85]

The most common conditions associated with CDI are dehydration and electrolyte disorders, which may affect up to 92% of patients. Less frequent conditions associated with CDI include septicemia, hypoalbuminemia, renal failure, septic shock, ascites and peritonitis. The more severe complications of CDI include intestinal perforation and toxic megacolon. While these severe complications are only observed in 0.1% to 3% of all CDI cases.[74,86,87], the mortality associated with toxic megacolon is high, ranging from 38% to 80%.[86,88]

Recurrence of CDI is seen in 10% to 20% of cases after initial symptom resolution (89). Recurrent infections are attributable to both relapse (i.e., spores that are not killed by antimicrobial therapy, which can then germinate once therapy is completed) and reinfection with a new strain.[90–93] However, it is important to note that patients who are asymptomatically colonized with *C. difficile* are at decreased risk for CDI, although the reason for this remains unclear.[94]

Exposure to antimicrobial agents and exposure to health care facilities are hallmark risk factors for CDI. While almost all antimicrobial agents have been associated with CDI, the most common are penicillins, second- and third-generation cephalosporins, clindamycin and fluoroquinolones.[84,95] As stated previously, advanced aged (>65 years) is also an important risk factor for CDI; this age group has over 10-fold the number of CDI hospitalizations than the general population in the United States.[74] Other, less well-defined risk factors for CDI include use of gastric acid suppressors, stool softeners, laxatives and/or enemas, chemotherapy and gastrointestinal surgery.[96]

Clostridium perfringens

Clostridium perfringens is ubiquitous in the environment and can be found in the feces of humans and animals. Food poisoning with *C. perfringens* requires ingestion of a high burden of vegetative cells, usually 10^8. The typical mechanism for this is food contaminated with *C. perfringens* that is improperly cooked, stored and reheated. Spores that survived the initial heating processes germinate and proliferate during a slow cooling of food or when the food is insufficiently reheated. Following ingestion, the organism sporulates upon entry into the small intestine, which is concomitant with expression of an enterotoxin that is responsible for patient symptoms. C. perfringens serotype A is the most common serotype associated with food poisoning and diarrhea.[97,98]

From 2009 to 2010, there were 60 confirmed *C. perfringens* foodborne outbreaks and 3,225 reported illnesses, making *C. perfringens* the second most common cause of bacterial foodborne disease in the United States in this time period.[28] Symptoms most often associated with *C. perfringens* food poisoning are watery diarrhea, severe abdominal cramping and pain and vomiting. The onset of symptoms ranges from 8 to 24 h after the ingestion of contaminated food. It is self-limiting and symptoms resolve within 24 h.

A rare type of food poisoning called enteritis necroticans or "pig-bel" is associated with the ingestion of food, usually pork, heavily contaminated with *C. perfringens* serotype C. This organism produces a beta toxin that causes intestinal wall necrosis. Pig-bel has a mortality rate of 40% and primarily affects malnourished persons, especially children.[99] *C. perfringens* has also been linked to antibiotic-associated diarrhea that does not cause pseudomembranous colitis.[73,100]

Escherichia coli

Escherichia coli was initially considered to only be a commensal residing in the gastrointestinal tract. However, several pathogenic variants (pathotypes) are now recognized and associated with diarrheal diseases

(Fig 1). Although *E. coli* is easy to identify to species level, it is extremely difficult to recognize strains belonging to different pathotypes of diarrheagenic E. coli, as these are defined by the expression of one or more group-specific virulence factors. The six major diarrheagenic pathotypes described to date are enteropathogenic was; *E. coli*, Shiga toxin-producing *E. coli* (STEC), enteroinvasive *E. coli* (EIEC), enterotoxigenic *E. coli* enteroaggregative *E. coli* and adherent invasive *E. coli*.[101] Of these, only (STEC) is routinely identified by most clinical and public health laboratories and it will be the focus of the discussion here. (STEC) is defined by the presence of a Shiga toxin 1 (Stx1) and/or Shiga toxin 2 (Stx2) gene. Historically, these isolates were called enterohemorrhagic E. coli (EHEC) or verocytotoxin-producing E. coli (VTEC). (STEC) includes both O157 and non-O157 serotypes of E. coli.

Ruminants, such as cattle, are the major reservoir for (STEC). Poor sanitation, fecal runoff into rivers and streams, and inadequate control measures in the meat and food processing industries have all led to the recovery of (STEC) from virtually any consumable product. Infection with (STEC) occurs following consumption of these contaminated products. Infections occur predominantly in the summer months but can be observed year-round.[102] By analyzing the genome of *E. coil* O157, scientists have determined that in the presence of certain genes host animals tend to shed much higher quantities of the bacteria than normal. Researchers have used genomics to show that has shown that these so-called "super-shedding "genes are also present in the strains of *E. coli* O157 that cause outbreaks in the humans; this finding supports the use of vaccination in cows (102,114). The incidence of (STEC) infections in the United States is monitored by FoodNet. In 2012, the incidence of O157 (STEC) was 1.12 per 100,000 population and the incidence of non-O157 (STEC) was 1.16 per 100,000.[103] Among the non-O157 (STEC) strains, O26, O103, O111, O121, O45 and O145 are the most common serotypes isolated in the United States.[104]

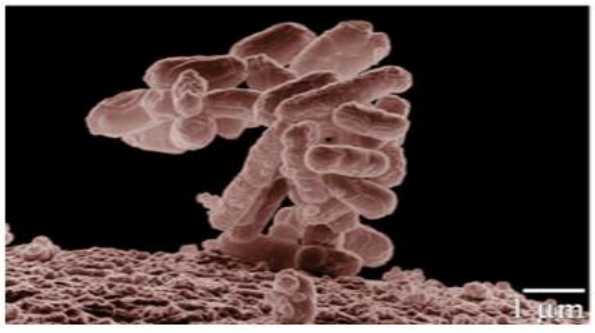

Figure:1
This scanning electron micrograph shows a cluster of E. Coil cells, which live in the guts of must mammals. Some strains of E. coli are benign, but others, like E. coli O157, produce toxic and cause gastrointestinal illness in human. (Credit: United Stated Department of Agriculture, via Wikimedia Commons)

The incidence of (STEC) is much higher in developing countries such as Argentina, India and Saudi Arabia but formal surveillance data are not available for these countries. Shiga toxin-producing *E. coli* (STEC) disease presents as enteritis that may quickly progress to hemorrhagic colitis. The toxin acts on the lining of the blood vessels, the vascular endothelium. The B subunits of the toxin bind to a component of the cell membrane known as glycolipid globotriaosylceramide (Gb3). Binding of the subunit B to Gb3 causes induction of narrow tubular membrane invaginations, which drives formation of inward membrane tubules for the bacterial uptake into the cell. These tubules are essential for uptake into the host cell. When the protein is inside the cell, the A subunit interacts with the ribosomes to inactivate them. The A subunit of Shiga toxin is an N-glycosidase that modifies the RNA component of the ribosome to inactivate it and so bring a halt to protein synthesis leading to the death of the cell (figure 2). The vascular endothelium has to continually renew itself, so this killing of cells leads to a breakdown of the lining and to hemorrhage. The first response is commonly a bloody diarrhea. This is because Shiga toxin is usually taken in with contaminated food or water.

Figure: 2
SLT2 from *Escherichia coli* O157:H7. The A subunit is Shown in red (top), and the B subunits, forming a pentamer, in different shades of blue *(bottom)* (112).

The toxin is effective against small blood vessels, such as found in the digestive tract, the kidney, and lungs, but not against large vessels such as the arteries or major veins. A specific target for the toxin appears to the vascular endothelium of the glomerulus. This is the filtering structure that is a key to the function of the kidney. Destroying these structures leads to kidney failure and the development of the often deadly and frequently debilitating hemolytic uremic syndrome. Food poisoning with Shiga toxin often also has effects on the lungs and the nervous system.[107] The chief symptoms included bloody diarrhea, abdominal pain, nausea and vomiting.[108] Importantly, not all (STEC) infections are associated with bloody diarrhea[109,110] and so laboratory

algorithms that only test bloody specimens for (STEC) are no longer considered standard of care. The most common and serious complication of (STEC) infection is the development of hemolytic-uremic syndrome (HUS), which typically presents 5 to 13 days after the onset of diarrhea.[110] (HUS) is life-threatening and consists of the triad of renal failure, microangiopathic hemolytic anemia and thrombocytopenia. The mortality rate connected with (HUS) is 3% to 5%.[111] It has been estimated that 61% of all (HUS) cases are related to (STEC) infection.[111] (HUS) has been observed more frequently in O157 (11% of cases) versus non-O157 (1% of cases) (STEC) infections.[104] Approximately 15% of children <10 years of age develop (HUS) following (STEC) infection. However, in the recent outbreak of O104 (STEC) in Germany, 22% of children developed (HUS).[112–114] It should be noted that this outbreak was caused by an atypical (STEC) strain that harbored enteroaggregative E. coli virulence factors in addition to the Shiga toxins. (HUS) occurs much less frequently among adults and is associated predominantly with advanced age (>75 years).[115] Increased rates of (HUS) have been more frequently associated with Stx2-expressing (STEC) strains. Exposure to antibiotics also increases the risk of (HUS) in children.[114] However, recent data demonstrated that treatment with ciprofloxacin reduced the risk of (HUS) in patients infected with the 2011 German O104 (STEC) strain.[116] These data are supported by a recent meta-analysis of studies between 1980 and 2011.[117] Despite this, the decision to treat a patient with (STEC) infection with antimicrobials remains controversial. In addition, use of antimotility agents has been associated with longer duration of bloody diarrhea, as well as progression to (HUS).[118]

Escherichia albertii

E. albertii was described as a new species in the genus Escherichia in 2003.[224] Most of the initial strains were misidentified as Hafnia alvei prior to the establishment of *E. albertii* as a species and were isolated from fecal samples from Bangladeshi children experiencing diarrheal illnesses. Subsequent evidence suggests that *E. albertii* is isolated fairly frequently from patients with diarrheal disease.[225,226] The organism harbors known enteropathogenic virulence factors are the presence of genes of the locus of enterocyte effacement (LEE), which contains the intimin gene (*eae*).[227,228] and has been associated with a major outbreak of gastroenteritis involving 48 persons.[229]

E. albertii grows well on routine enteric agars, is frequently misidentified biochemically as, Salmonella, Citrobacter, or inactive E. coli strains[230] and may not be included in the databases of commercial identification systems. The important phenotypic features distinguishing *E. albertii* from *E. coli* include a negative indole reaction and inability to ferment lactose, d-sorbitol and d-xylose.[224] Phylogenetic studies indicate that *Shigella boydii* type 13, already known not to belong to the true *shigellae*, is, in fact, a member of the species *E. albertii*.[227] In the 10th edition of the Manual of Clinical Microbiology, the species is broken down into two biogroups. Biogroup 1 represents the *original E. albertii* strains and biogroup 2 represents isolates formerly referred to as S. boydii 13. *E. albertii* can be identified by 16S rRNA gene sequencing and by matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS).

Listeria monocytogenes

The genus Listeria is composed of six species, of which *Listeria monocytogenes* is the common human pathogen, causing intestinal as well as extra intestinal infections. *L. monocytogenes* is a common environmental inhabitant of soil, vegetation, and animals.[119] Because *Listeria spp*. can survive under acidic and salt-enhanced conditions in foods and can grow at refrigeration temperatures (4°C), they have the capacity to survive and multiply in large numbers in a variety of refrigerated foods.[119,120] A high percentage (32%) of foods recalled by the FDA involve *L. monocytogenes*.[121] The major risk factor associated with L. monocytogenes gastroenteritis is the consumption of foods heavily contaminated (10^7 to 10^9 CFU/g or ml) with this bacteria.[122] The incidence of *L. monocytogenes* gastroenteritis is unknown, but the Surveillance data from the CDC and other sources, including Food Net, have focused on invasive listeriosis (bacteremia and central nervous system infection) as a consequence of foodborne infection. In 2011, the incidence of invasive listeriosis was 0.31 per 100,000 population. Many patients with invasive listeriosis have a history of gastrointestinal symptoms that consist of diarrhea, nausea, vomiting and fever. This, coupled with reports of *L. monocytogenes* outbreaks of gastroenteritis, suggests that *L. monocytogenes* may be an infrequent cause of gastroenteritis in patients with negative bacterial stool cultures.[122,123] One 2015 Canadian study found the maximum incidence of L. monocytogenes-associated diarrhea to vary from 0.2% to 0.5%, depending upon the population studied.[123] On rare occasions, *Listeria ivanovii* has been reported to cause diarrhea in severely immunosuppressed individuals.[124]

The typical incubation period for gastrointestinal infection is 24 h; however, it can range from 6 h to as long as 10 days.[120] Once symptoms begin, diarrhea lasts for 1 to 3 days. In a study of cases of gastroenteritis linked to outbreaks, attack rates ranged from 50% to 90% and the median number of stools/day was 12 (range, 3 to 50).[122] The syndrome is typically characterized by a febrile illness with diarrhea, headache and arthralgia/myalgia. Other, less frequently encountered complications include abdominal pain, nausea, vomiting, dizziness, lymphadenopathy and presence of a rash.[12,122] Fever, which occurs in 60% to 100% of infected persons, is a cardinal feature associated with *L. monocytogenes* diarrhea. The most serious complication of listeriosis is invasive disease, including septicemia and meningitis.

L. monocytogenes has tropism for the brain and as a result can cause encephalitis, rhombencephalitis (brain stem encephalitis), and brain abscess. The case fatality rate for most cases of listeriosis with comorbidities has been reported to be between 20% and 40%.[125]

Reputed risk factors associated with acquiring L. monocytogenes gastroenteritis include gastric acidity, use of antacids, use of H_2 receptor antagonists, and use of laxatives.[119,122,126] In addition, those with inflammatory bowel disease (IBD) and Crohn's disease may have a more frequent incidence of Listeria diarrhea (as opposed to Campylobacter or Salmonella).[123,126]

Plesiomonas shigelloides

Plesiomonas shigelloides is the sole oxidase-positive member of the Enterobacteriaceae family. While *P. shigelloides* has been associated with diarrheal disease in numerous reports, a definitive causal relationship with *P. shigelloides* has yet to be established through volunteer or animal studies.[127]

P. shigelloides is found in aquatic environments and has been isolated from both cold-blooded and warm-blooded animals. In humans, there has been a reported prevalence rate of 0.01% to 5.5% in asymptomatic individuals.[128,129] Transmission occurs primarily through the consumption of seafood, such as oysters and shellfish, or water that has been contaminated with sewage. Most cases of *P. shigelloides* diarrheal illness are sporadic; however, there have been reported outbreaks associated with the organism.[130–132] Coinfection with *P. shigelloides* and other enteropathogens has been reported[132,133] and some evidence suggests that *P. shigelloides* causes diarrhea only as a coinfecting pathogen, rather than on its own.[133] Both secretory and dysentery-type diarrhea have been reported with *P. shigelloides* infections.[130,134] Most infections are characterized by self-limiting diarrhea with blood or mucus, abdominal cramps, vomiting and fever.[130] While most diarrheal episodes are described as acute, there have been reported chronic cases lasting over 2 weeks.[135]

Salmonella Species

Salmonella, a member of the family Enterobacteriaceae, is a facultatively anaerobic Gram-negative rod. Salmonella taxonomy is a complicated matter, with two species in the genus: *Salmonella enterica* and *Salmonella bongori*. Salmonella enterica has six subspecies *(S. enterica* subsp. *enterica*, *S. enterica* subsp. *salamae*, *S. enterica* subsp. *arizonae*, *S. enterica* subsp. *diarizonae*, *S. enterica* subsp. *indica* and *S. enterica* subsp. *houtenae*). Because of the diversity of the genus, several isolates may be difficult to identify due to atypical biochemical reactions, that can be further serotyped using the Kauffmann-White-Le Minor scheme, based on the properties of their somatic (O), flagellar (H) and capsular polysaccharide (Vi) antigens. There are over 2,500 serotypes of S. enterica.[136,137]

Salmonella colonizes the intestinal tracts of vertebrates. Some serotypes, including *Salmonella enterica* subsp. enterica serotype *Typhi* (Salmonella Typhi), are only found in human hosts. The majority of Salmonella cases occur as the result of ingesting contaminated food or water. Salmonella can also be acquired by contact with domestic animals and their food products, farm animals or animals in petting zoo and exotic pets like turtles, hedgehogs and iguanas.[138–142] Salmonella can also be transmitted from person to person via the oral-fecal route.

The incidence of Salmonella infections in the United States in 2011 was 1,645 per 100,000 population[143], with higher rates in late summer and early fall. Worldwide, there are an estimated 94 million cases of nontyphoidal Salmonella gastroenteritis and about 155,000 deaths.[144] In developing countries and the Indian subcontinent in particular, typhoidal isolates cause the majority of disease and are associated with an estimated 21.6 million annual cases and 216,500 deaths.[145] In sub-Saharan Africa, nontyphoidal Salmonella, predominantly the *Salmonella Typhimurium* ST313 strain, are a significant cause of bloodstream infections in both children and adults.[146,147] In the United States, the most common serotypes reported are *Salmonella Enteritidis, Salmonella Typhimurium and Salmonella Newport*.[143] In Saudi Arabia, the most common serotypes reported are *Salmonella Typhimurium* and *Salmonella Enteritidis*.[148]

Nontyphoidal salmonellosis consists of diarrhea, nausea, headache, and abdominal cramps, which last for 4 to 7 days. Fever may be present and usually resolves in 24 to 48 h. The disease is typically limited to the lamina propria of the small intestine and antimicrobial therapy is not indicated. Extraintestinal manifestations, such as bacteremia, septic arthritis, urinary tract infections and osteomyelitis, are seen in 5% of cases.[153] Some individuals may become asymptomatic carriers of the organism and shedding occurs for several weeks to a few months. The established genetic and pathogenic differences among S. enterica serotypes, particularly Typhi and nontyphoidal serotypes NTS, warrant further characterization of salmonella cytolethal distending toxin S-CDT among different NTS serotypes.[150]

Typhoid fever is caused by *Salmonella Typhi* and a similar syndrome is caused by *Salmonella Paratyphi* A, *Salmonella paratyphi* C (strain RKS4594) gene ccdB and tartrate-negative variants of *Salmonella Paratyphi* B. In typhoid, the organism disseminates from the lamina propria to the reticuloendothelial system in infected phagocytes via lymphatic and hematogenous routes. Fever, malaise, anorexia, headaches and vomiting are common symptoms of typhoid and typically start 1 to 3 weeks after infection. Patients may have diarrhea following ingestion of the organism, but many do not. Rose spots, which are blanching maculopapular lesions 2 to 4 mm in diameter, are seen in 5 to 30% of cases. A

complication of untreated typhoid fever is the erosion of the blood vessels in the Peyer's patches, which can lead to intestinal hemorrhage.[145] The organism persists in the mesenteric lymph nodes, gallbladder and bone marrow for years. Five to 10 percent of patients will have a relapse of infection, typically 2 to 3 weeks following resolution of symptoms and Up to 10% of asymptomatic patients will become carriers and 1 to 4% of these will shed for more than 1 year.[154]

The severity of Salmonella disease depends on the inoculating dose[155], infecting serotype[151] and predisposing host factors. Children under 1 year of age have the highest incidence of Salmonella in the United States[143] Because Salmonella must survive the gastric acid barrier in order to gain access to the small intestine where it causes disease, patients with decreased gastric acid production, from advanced age, gastrectomy, or H2 receptor antagonists, are at increased risk of infection. Individuals with impaired cellular immunity (e.g., AIDS) or altered phagocyte function (e.g., sickle cell anemia) are at increased risk for both invasive nontyphoid Salmonella infections and typhoid.[156,157] However, these individuals do not appear to have more severe typhoid infections should they become infected.[158,159] In the United States, nearly all cases of typhoid and paratyphoid fever are in returning travelers and immigrants.[160]

Shigella Species

Shigella species are host adapted to humans but have been documented in rare instances from dogs and primates.[161] They can be acquired from ingestion of a variety of foods or water contaminated with human feces, or by laboratory workers. The four species of Shigella are *Shigella dysenteriae, Shigella flexneri, Shigella boydii* and *Shigella sonnei*. Transmission by person-to-person contact is common for Shigella spp. because of a low infectious dose of 10 to 100 organisms.[161] Between 2009 and 2010, Shigella accounted for 508/8,523 (2%) of reported illnesses associated with foodborne outbreaks.[28] The incidence of Shigella infections reported by FoodNet in the United States in 2011 was 3.24 per 100,000 and ranged from 0.99 to 6.78 per 100,000, depending on the region.[143]

Shigellosis and dysentery are diseases associated primarily with poor hygiene and lack of access to medical care. Approximately 150 million cases are reported annually in developing countries, in contrast to 1.5 million cases in industrialized nations. Of importance, one multicenter study found that half of patients with culture-negative, bloody stools were positive by PCR for Shigella, suggesting that the actual incidence of Shigella is grossly underestimated.[162] Shigellosis symptoms range from watery diarrhea to mucoid and/or bloody stools, which can be accompanied by fever, malaise and abdominal pain. In one study of 1,114 culture-confirmed patients followed for 14 days or longer, 29%[241] reported diarrhea persisting for ≥14 days.[162] The Shiga toxin (Stx), also called the verotoxin, is produced by *Shigella dysenteriae*. Factors associated with persistence were age, fever, mucoid diarrhea, vomiting and abdominal pain. Headache and nuchal rigidity are common, with 95% and 39% of patients reporting these symptoms, respectively.[161] *S. dysenteriae* type1 is responsible for classic dysentery, which is manifested by fever, abdominal cramping and bloody stool. Sepsis occurs primarily in malnourished pediatric patients in developing countries and is most commonly caused by *S. flexneri*, long-term carriage (>1 year) occurs but is rare.[163,164]

Meningitis, pneumonia and urinary tract infections (UTIs) are rare complications of shigellosis and are most commonly seen with *S. flexneri* and *S. sonnei*.[165–167] Notably, 40% of UTIs are asymptomatic and 35% are culture negative.[167] Reactive arthritis has been reported in 1 to 3% of cases from outbreak data.[161] The onset of reactive arthritis occurs within 3 weeks of gastrointestinal symptoms, with the duration of symptoms ranging from a few days to a few months; only *S. flexneri* has been associated with reactive arthritis.

(HUS) is the most serious complication of shigellosis, occurs in ∼13% of cases of *S. dysenteriae* type 1. Shigellosis and is attributable to the expression of Stx1 by this organism.[168] However, in rare cases, non-S. dysenteriae species of Shigella have been isolated from children with (HUS), *S. dysenteriae* type 1 (HUS) is seen mainly in children <5 years old in Asia and Africa.[168,169]

Staphylococcus aureus

S. aureus food poisoning is an intoxication caused by the ingestion of preformed, heat-stable enterotoxin *Staphylococcus aureus* produces a wide variety of toxins including staphylococcal enterotoxins (SEs; SEA to SEE, SEG to SEI, SER to SET) with demonstrated emetic activity and staphylococcal-like (SE*l*) proteins, which are not emetic in a primate model (SE*l*L and SE*l*Q) or have yet to be tested (SE*l*J, SE*l*K, SE*l*M to SE*l*P, SE*l*U, SE*l*U2 and SE*l*V). SEs and SE*l*s have been traditionally subdivided into classical (SEA to SEE) and new (SEG to SE*l*U2) types. All possess superantigenic activity and are encoded by accessory genetic elements, including plasmids, prophages, pathogenicity islands, *v*Sa genomic islands, or by genes located next to the staphylococcal cassette chromosome (SCC) implicated in methicillin resistance. SEs are a major cause of food poisoning, which typically occurs after ingestion of different foods,/ there are 21 known staphylococcal enterotoxins, but phage-encoded staphylococcal enterotoxin A is the most frequently reported cause of S. aureus food poisoning worldwide.[170–172] Coagulase-negative staphylococci (CoNS) can also acquire enterotoxins, but the reported cases or outbreaks of CoNS food poisoning have been limited.[173,174] *S. aureus* is ubiquitous in the environment and colonizes the skin and mucous membranes of many mammals and birds.[175] In humans, the anterior nares is

the most commonly colonized site and the organism is shed on to healthy skin.[176] The rate of persistent carriage of *S. aureus* is reported to be 10 to 35% and the rate of intermittent colonization ranges from 20 to 75%.[176,177] For those individuals harboring *S. aureus*, the organism can be transferred from their hands while preparing food. *S. aureus* is most commonly found in foods such as cream-filled pastries, cream pies and sandwich fillings. However, food products involved in *S. aureus* food poisoning differ widely from one country to another.[175] The CDC estimates that there are approximately 241,000 cases of foodborne illnesses in the United States caused by *S. aureus* annually.

A rapid onset of symptoms is characteristic of *S. aureus* food poisoning. General malaise, nausea, vomiting, stomach cramps and diarrhea can occur within 30 min of ingestion of the contaminated food. The typical incubation period is 2 to 7 h, with symptoms resolving in about 12 h.[11] Patients with staphylococcal food poisoning are not febrile. In most cases, medical treatment is not required. However, hospitalization for the severity of symptoms may be seen in 10% of those with *S. aureus* food poisoning.[178] Severe dehydration may be seen in young children and elderly patients.[178]

S. aureus food poisoning requires consumption of food or beverages harboring the staphylococcal enterotoxins. Unsafe food handling practices, including neglecting to wash hands prior to handling food and to promptly refrigerate prepared foods, are the primary reason for intoxication.

Vibrio and Vibrio-Like Species

The genus Vibrio is currently comprised of over 60 species. A number of other species traditionally associated with this genus have been recently reclassified into phylogenetically related neighboring clades, including Grimontia hollisae (Vibrio hollisae). Of the more than 60 Vibrio or Vibrio-like species that have been described, only a few these taxa have been consistently associated with bacterial gastroenteritis, with the two major species being *Vibrio cholerae* and *Vibrio parahaemolyticus.* Less frequent, but still of concern, are *Vibrio mimicus*, *Vibrio fluvialis*, *Vibrio vulnificus*, and *G. hollisae.*

Vibrio and vibrio-related bacteria are widely distributed in saltwater environments with salt concentrations of 17 to 37 ppt. Freshwater habitats with low salt concentrations (<0.5 ppt) can harbor nonhalophilic Vibrio spp. such as *V. cholerae and V. mimicus*. Because of their intimate association with the marine environment, Vibrio spp. can be found in many inhabitants of this macroecosystem, including shellfish such as oysters, clams, shrimp and scallops.

The preeminent pathogen of this group is *V. cholerae*, which can cause sporadic, epidemic and pandemic cholera. The WHO estimates that over 1.4 billion persons worldwide are at risk of developing cholera each year, with an estimated 2.8 million cases occurring annually and with over 130,000 deaths.[179,180] Today, the highest incidence of cholera is found in Africa and the southern regions of Asia. Two serogroups of *V. cholerae*, O1 (El Tor biotype) and O139, are responsible for the ongoing pandemic of cholera disease.

Cholera is not common in the United States, but the incidence of vibriosis (*V. parahaemolyticus, V. vulnificus* and *V. alginolyticus)* is increasing. There are an estimated 80,000 illnesses with 500 hospitalizations and 100 deaths each year due to Vibrio illnesses in the United States, based upon data submitted through the Cholera and Other Vibrio Illness Surveillance (COVIS) system and Food Net.[181,182] These cases include not only patients with diarrhea but also those with primary septicemia, wound infections and otitis externa caused by Vibrio spp. The annual incidence of vibriosis in the United States has increased from 0.09 to 0.15 per 100,000 population in 1996 to 0.28 to 0.42 per 100,000 in 2010, with the highest incidence in coastal areas.[181]

V. parahaemolyticus is responsible for many outbreaks of food-associated gastroenteritis worldwide. In Japan, it has been one of the most important causes of foodborne diarrhea since the 1960s.[183] This species has also been responsible for the global spread of a pandemic clone, O3:K6, causing gastroenteritis in such diverse locales as North, Central and South America, the Indian subcontinent, parts of Africa and Europe and Indonesia from 1996 through 2004.[184] Other clonal strains, such as O4:K12, have caused more restricted outbreaks of disease, such as on the west coast of the United States.[185] *V. mimicus* has been reported to cause at least two outbreaks of diarrheal disease.[186,187] The number of studies and case reports worldwide describing gastrointestinal infections cause by *V. fluvial* is seems to be increasing as well, In the United States, V. fluvialis is typically the third most common Vibrio species associated with gastroenteritis, following *V. parahaemolyticus* and non-O1, non-O139 *V. cholera.*[188,189]

The chief clinical features of cholera are an afebrile, painless, watery diarrhea associated with *V. cholerae* O1 El Tor infection, accompanied by multiple bowel movements over a short period of time. Incubation periods for cholera typically span from 18 h to 5 days, asymptomatic colonization is relatively common in areas of endemicity due to constant exposure to the infecting agent under unsanitary conditions. For symptomatic persons, clinical presentations of cholera range from a mild to moderate diarrhea to a more fulminant form termed cholera gravis.[190] Cholera gravis is characterized by the release of large volumes of water (500 to 1,000 ml/h), which rapidly leads to severe dehydration, shock and death over a short period of time if left untreated. The more severe forms of cholera are associated with pandemic strains bearing the O1 serogroup that carry a series of virulence genes, the two most important of

which are those for cholera toxin and toxin-coregulated pilus.[191] Cholera toxin is typically only found in O1 El Tor or the epidemic O139 Bengal strains, although other serogroups (O75 and O141) occasionally harbor these elements as well and produce cholera-like disease.

Gastroenteritis caused by non-O1, non-O139 serogroups of *V. cholerae* is typically milder and self-limiting, since they normally lack the cholera toxin gene. These non-O1, non-O139 isolates nevertheless cause the vast majority of V. cholerae gastrointestinal infections in the United States. While disease caused by these isolates is typically mild, fatal cases of non-O1, non-O139 *V. cholerae* can occur.[192]

V. parahaemolyticus is the most common cause of Vibrio-associated diarrhea in the United States. The most frequent symptoms linked to *V. parahaemolyticus* enteritis include diarrhea with abdominal cramps, with approximately half of all infected individuals having a febrile illness.[193] Two prominent symptoms, nausea (76%) and vomiting (55%), help to distinguish diarrhea caused by this species from other vibriosis or other enteritides associated with bacteria.

Unlike with many other enteric pathogens, secondary complications due to Vibrio gastroenteritis are rare. The principle complication that can arise from enteric infection is secondary spread to the bloodstream, producing septicemia. In the case of *V. cholerae*, virtually all such bacteremia are caused by non-O1, non-O139 isolates.[194] Other, infrequently encountered Vibrio species that have been demonstrated to cause septicemia subsequent to primary gastrointestinal infections include *V. fluvialis* and *V. hollisae*.[195,196]

In the case of cholera, most infections arise in areas of endemicity through contaminated water and nonhygienic conditions which perpetuate persistence of O1. However, persons can also develop cholera through ingestion of contaminated shellfish or seafood products containing high concentrations of *V. cholerae*. For other Vibrio and Vibrio-like infections, the two major risk factors for acquiring disease are consumption of contaminated seafood and foreign travel. Vibrio spp. have naturally been recovered from many different types of seafood, including oysters, mussels, clams, shrimp and tilapia.[197] A large number of seafood vehicles have been implicated in vibriosis outbreaks associated with non-V. cholerae vibrios.[186,193]

Yersinia enterocolitic and Yersinia pseudo tuber-culosis

There are currently 18 species within the genus Yersinia, nine of which are isolated from humans. *Yersinia enterocolitica*, the most well-established enteropathogen of the genera, has two subspecies described, *Y. enterocolitica* subsp. *enterocolitica* and *Y. enterocolitica* subsp. *paleartica*, which can be distinguished by sequencing of the 16S rRNA gene.[198] *Y. enterocolitica* subsp. *paleartica* O:3/4 is the dominant serotype worldwide.[199] Yersinia pseudotuberculosis is also enteropathogenic but is more commonly associated with sepsis. *Y. frederiksenii, Y. kristensenii, Y. intermedia, Y. mollarettii, Y. bercovieri, and Y. rohdei* can be isolated from humans (including patients with diarrhea), but they are not believed to be pathogenic except in rare cases in individuals with underlying disorders.[161,200] Pathogenic strains of Y. enterocolitica are determined by the biotype and serotype.

Y.enterocolitica and *Y.pseudotuberculosis* can be isolated from a host of animals, birds, foods and environmental sources.[201] Animal sources of human infections include hares, rodents, cats (*Y. pseudotuberculosis*) and dogs (*Y. enterocolitica*). Environmental sources include soil, water and sewage.[161] Pigs are a major reservoir for both *Y. enterocolitica*, *Y. pseudotuberculosis* infections worldwide.[201–203]

Between 1996 and 1999, FoodNet determined an annual incidence of *Y. enterocolitica* in the United States of 1.0/100,000 persons, with the greatest rates of infection in blacks and Asians.[203] Between 1996 and 2009, FoodNet active surveillance noted a decline in the overall annual incidence (0.5/100,000 persons) of *Y. enterocolitica*, with rates in blacks also declining from 3.9 to 0.4 per 100,000 by 2009.[203] The overall rate of Y. enterocolitica reported by FoodNet in 2011 was 0.34 per 100,000.[143] The high infection rate in blacks has been associated with homemade chitterlings (pork intestines) and educational efforts have been cited as a possible explanation for the decrease in infections in this ethnic group. Infection rates are highest in children.[201] In the United States, 32% of cases occurred in children <1 year old and 47% in children <5 years old.[203] Similar epidemiology is seen outside the United States; in China, 44% of cases are reported in children <3 years of age.[202] *Y. enterocolitica* infections are classically documented to occur in the autumn and winter; however, a study of yersiniosis in Europe conducted over a 3-year period found no clear seasonal pattern.[201,202] and winter trends in yersiniosis in high-risk populations have also diminished in the United States.[203]

Y. pseudotuberculosis most commonly causes mesenteric adenitis, which manifests as an appendicitis-like syndrome with fever and right lower quadrant abdominal pain. Y. pseudotuberculosis can also cause severe septicemia.[161] Symptoms associated with sepsis include fever, diarrhea, abdominal pain or tenderness, anorexia, nausea, vomiting, and malaise. Mortality rates range from 28% to 100% in treated and untreated cases, respectively.[161]

Y. enterocolitica gastrointestinal disease ranges from self-limiting enteritis with diarrhea, low-grade fever and abdominal pain to severe disease such as terminal ileitis and mesenteric lymphadenitis which also mimics appendicitis.[203–205] Onset is generally 24 to 48 h

following ingestion, with illness lasting between 7 and 14 days, but symptoms may persist for up to 2 to 12 months.[201,205] Bloody stools occur in 20 to 46% of cases and host susceptibility, number of ingested organisms and serotype are determining factors for severity of disease.[201] Severe cases may require hospitalization due to dehydration; in one study, 27% of 571 patients were hospitalized.[205]

Sepsis is uncommon and is often associated with cardiovascular, dermal, or pulmonary conditions and abscesses. Pharyngitis, with sore throat and fever as the predominant symptoms, is not unusual in yersiniosis; in one multistate outbreak, 14 of 172 (8%) patients reported pharyngitis. Fulminant symptoms, including difficulty swallowing and breathing, may occur and require immediate medical attention.[161] In these cases, *Y. enterocolitica* can be isolated from throat cultures.

The two most common sequelae of *Y. enterocolitica* infection are reactive arthritis and erythema nodosum, an immunologically mediated disease resulting in inflammation of subcutaneous adipose tissue with eruption of painful nodular lesions.[205] In one large study of 571 patients, 7% and 3% of 571 patients reported reactive arthritis or erythema nodosum, respectively.[205] The onset of reactive arthritis generally occurs <3 weeks after enteritis and the longer the duration of gastrointestinal symptoms, the greater the likelihood that reactive arthritis will develop.[161] Joint inflammation generally subsides spontaneously after 1 to 12 months, but 10% of patients will develop chronic arthritis.[206] Approximately 80% of patients developing reactive arthritis carry the HLA-B27 allele.[206] Septic arthritis is less commonly encountered and is not associated with HLA-B27.[161]

Because some *Y. enterocolitica* serotypes are unable to synthesize siderophores (compounds that sequester iron from the host), patients with iron overload disease are more susceptible to infection.[161,201] *Y. enterocolitica* can be acquired from blood transfusions, as the organism readily grows at lower temperatures used to store blood products. The development and severity of disease are dependent on the species of Yersinia (other than Y. enterocolitica) and the Y. enterocolitica bioserotype acquired.[200,204,207]

Bacteroides fragilis

Strains of *B. fragilis* carrying an ~6-kb pathogenicity island produce a zinc metalloprotease enterotoxin that has been known by several different names, including B. fragilis toxin and fragilysin.[208,209] These enterotoxigenic *B. fragilis* strains (ETBF) not only have been implicated as a cause of diarrheal disease in children under 5 years of age but more recently have been associated with inflammatory diarrhea in children and adults.[210] A meta-analysis of 17 studies that evaluated the association of ETBF with diarrheal disease found that 12 (71%) of the studies demonstrated a higher frequency of ETBF in patients with diarrhea than in controls.[211] In contrast, a recent Indian study found no difference in the rate of isolation of ETBF as a sole pathogen from children with and without diarrhea.[212] This suggests that other, mitigating factors may play a role in the infective process for ETBF.

Currently, there is no easy method to detect ETBF. Potential *B. fragilis* isolates can be recovered from stool on Bacteroides bile esculin agar (Becton Dickinson, Sparks, MD) and then tested for enterotoxigenicity *in vitro* using PCR for the Bacteroides fragilis toxin gene (*bft*).[212] Alternatively, the cytopathic effect (CPE) produced by fragilysin on HT29/C1 (human colon) cell lines can be evaluated.[211] Both methods are employed only for research purposes at this time.

Edwardsiella tarda

E. tarda is one of four species currently residing in the genus *Edwardsiella* of the family Enterobacteriaceae and is the only species considered pathogenic for humans. A common inhabitant of fish, reptiles, marine animals and aquatic birds.[213,214], *E. tarda* can also be recovered from water. Approximately 80% of reported human illnesses attributed to *E. tarda* involve infections of the gastrointestinal tract.[213] Data from a number of studies suggest that E. tarda is associated with 0.3% to 1.0% cases of gastroenteritis.[161,213] Asymptomatic carriage of *E. tarda* has been reported.[213]

E. tarda-associated diarrhea can present in one of several forms, the most common of which is watery diarrhea. Other diarrheal syndromes linked to *E. tarda* include dysentery, chronic diarrhea and enteric fever.[213,215] Risk factors for acquiring *E. tarda* diarrhea include consumption of contaminated fish or seafood, accidental ingestion of contaminated water, exposure to water from ornamental aquariums and handling pet turtles.[216–221] Person-to-person transmission has also been postulated but currently remains unsubstantiated.[222] Two populations thought to be particularly susceptible to E. tarda infection are persons >50 years of age and young children <5 years of age.[213,223]

Klebsiella oxytoca

Since the late 1970s and early 1980s, K. *oxytoca* has been sporadically linked to cases of antibiotic-associated hemorrhagic colitis in Japan and other locations around the world.[231] In 2006, in an elegant series of clinical observations and histopathological studies on six patients with antibiotic-associated hemorrhagic colitis (AAHC) convincingly established *K. oxytoca* as the etiological agent in persons negative for *Clostridium difficile*.[232] C. difficile-negative patients who are at higher risk of developing *K. oxytoca* colitis include those previously receiving penicillins or on nonsteroidal anti-inflammatory drugs.[232] At present, confirmation of *K. oxytoca* colitis in *C. difficile*-negative patients requires detection of the species-specific K. oxytoca cytotoxin by detection of CPE on HEp-2, CHO, or HeLa cells.[232–234]

In a recent study of 5,581 stool specimens submitted for *C. difficile* testing at an acute-care health system in China, 2.1% of specimens harbored *K. oxytoca*, but only 29.1% of these strains were cytotoxin producing.[235]

A second highly suggested, but unproven, syndrome attributed to *K. oxytoca* is diarrhea. Although one study found no correlation between the presence of *K. oxytoca* and diarrhea[236], a later study found a high percentage of cytotoxin-positive *K. oxytoca* isolated from patients with health care-associated diarrhea that did not develop into AAHC.[235] In the latter study, a specific selective medium termed SCITB (Simmons citrate-inositol-tryptophan-bile salts) was developed to recover *K. oxytoca* from stools. This medium has been shown to improve the recovery of *K. oxytoca* over that with MacConkey (MAC) agar by 30%.[235] This medium could greatly aid in determining the significance of *K. oxytoca* from mild to moderate cases of diarrhea.

Table 1: Common bacteria cuasing foodborne illness, symptoms, common food sources and there incubatin period. (WHO 2015)

Microorganism	Food–borne illness	Symptoms	Common food sources	Incubation period
Staphylococcus aureus	Intoxication	Nausea, vomiting, abdominal cramping	Foods contaminated by improper handling and holding temperatures—meats and meat products, poultry and egg products, protein-based salads, sandwich fillings, cream-based bakery products	1–12 hours
Salmonella species	Infection	Abdominal cramps, diarrhea, fever, headache	Foods of animal origin; other foods contaminated through contact with feces, raw animal products, or infected food handlers. Poultry, eggs, raw milk, meats are frequently contaminated.	12–72 hours
Escherichia coli group	Infection	Watery diarrhea, abdominal cramps, low-grade fever, nausea, malaise	Contaminated water, undercooked ground beef, unpasteurized apple juice and cider, raw milk, alfalfa sprouts, cut melons	12–72 hours
Shigella	Infection	Fever, abdominal pain and cramps, diarrhea	Fecally contaminated foods	12–48 hours
Campylobacter jejuni	Infection	Diarrhea, perhaps accompanied by fever, abdominal pain, nausea, headache, and muscle pain	Raw chicken, other foods contaminated by raw chicken, unpasteurized milk, untreated water	2–5 days
Bacillus cereus	Intoxication	Watery diarrhea and cramps, or nausea and vomiting	Cooked product that is left uncovered _milk, meats, vegetables, fish, rice, and starchy foods	0.5–15 hours
Clostridium perfringens	Infection	Intense abdominal cramps, diarrhea	Meats, meat products, gravy, Tex-Mex type foods, other protein-rich foods	8–24 hours
Clostridium botulinum	Intoxication	Lethargy, weakness, dizziness, double vision, difficulty speaking, swallowing, and/or breathing; paralysis; possible death	Inadequately processed, home-canned foods; sausages; seafood products; chopped bottled garlic; kapchunka; molona; honey	18–36 hours
Listeria Monocytogenes	Infection	Nausea, vomiting, diarrhea; may progress to headache, confusion, loss of balance and convulsions; may cause spontaneous abortion	Ready-to-eat foods contaminated with bacteria, including raw milk, cheeses, ice cream, raw vegetables, fermented raw sausages, raw and cooked poultry, raw meats, and raw and smoked fish	Unknown; may range from a few days to 3 weeks

Providencia alcalifaciens

A British survey of travelers to Mediterranean countries between 1987 and 1988 found a significant association between the recovery of *P. alcalifaciens* and diarrheal disease.[237] These initial findings have been subsequently supported by other studies describing individual cases of *P. alcalifaciens*-associated diarrhea and at least three outbreaks of gastrointestinal disease, including one large outbreak involving >270 children in Japan.[238–240] *P. alcalifaciens* strains implicated in diarrheal disease are invasive in HEp-2 cell monolayers, although the type of diarrhea that they produce is secretory[239,241]; some strains additionally produce a cytolethal distending toxin.[242] Persons most at risk of developing *P. alcalifaciens* diarrhea are those who are involved in foreign travel or have consumed contaminated foods containing the organisms.[237,243]

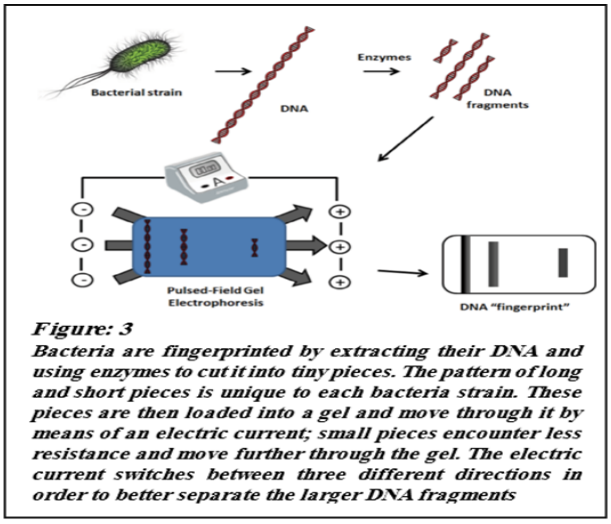

Figure: 3
Bacteria are fingerprinted by extracting their DNA and using enzymes to cut it into tiny pieces. The pattern of long and short pieces is unique to each bacteria strain. These pieces are then loaded into a gel and move through it by means of an electric current; small pieces encounter less resistance and move further through the gel. The electric current switches between three different directions in order to better separate the larger DNA fragments

Most isolates of *P. alcalifaciens* recovered from diarrheal stools have been isolated in pure culture, as predominant flora, or without any other recognizable enteropathogens being detected.[237,240,243] A selective medium, termed PAM (Providencia alcalifaciens medium), has been described for the recovery of this species from feces.[244] This medium has subsequently been modified as PMXMP (polymyxin-mannitol-xylitol medium for Providencia) and used with success.[242,243]

Phenotypic and molecular subtyping

Phenotypic as well as molecular subtyping methods have been key tools in food safety and have played important roles for foodborne disease outbreak detection, identification of pathogen sources responsible for food contamination through the food chain and source attribution. Traditional phenotypic subtyping methods include most prominently serotyping as well as phage typing and biotyping, to name a few. The development of molecular and nucleic acid-based subtyping methods has revolutionized the field of subtyping. Molecular subtyping methods used for foodborne pathogens can be divided into banding pattern-based methods [e.g., pulse field gel electrophoresis (PFGE); ribotyping; repetitive extragenic palindromic sequence (REP)-PCR] as well as sequencing-based subtyping [e.g., multilocus sequence typing (MLST) and multiple-locus variable number tandem repeat analysis (MLVA)].

Importantly, many molecular subtyping methods allow for more sensitive discrimination than traditional phenotypic methods (e.g., a single *Salmonella* serotype may be differentiated into 20+ PFGE types). These methods often also allow for more reproducible subtyping compared with traditional methods(Figure3).[251]

A turning point for molecular subtyping use for bacterial foodborne disease surveillance was the establishment of PulseNet in the U.S. in 1996. This network initially focused on subtype characterization of *Escherichia coli* O157:H7 but was subsequently expanded to other pathogens as shown in figure 4.[252]

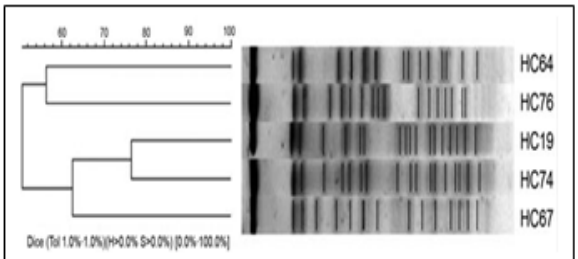

Figure 4: Image from the gel shows the unique fingerprint obtained by pulsed-field gel electrophoresis for various strains of E coli. (Credit United States Centers for Disease control and prevention)

This system has also expanded internationally as "PulseNet International." Key innovations with PulseNet include the development and implementation of a highly standardized subtyping method for bacterial pathogens, based on PFGE separation of whole-genomic restriction digests, as well as rapid Web-based exchange of the resulting PFGE patterns. This approach has provided tremendous improvements in the ability to detect temporally and spatially distributed foodborne disease outbreaks as shown in (figure5). While the tremendous food safety impact of PulseNet and other molecular subtyping methods is well recognized, there is no doubt that the rapidly emerging use of whole-genome sequencing (WGS) for foodborne pathogen subtyping will provide another major improvement in our ability to detect foodborne disease outbreaks and define pathogen sources throughout the food chain. Importantly, even though WGS provides for virtually complete characterization of bacterial isolates and maximum resolution for DNA-based characterization, data interpretation can and will still be challenging, particularly if one aims to establish whether two isolates that are genetically identical (or have only one or a few genetic differences) share a recent enough common ancestor to establish a cause-and-effect-type relationship. To illustrate, WGS of *Listeria monocytogenes* isolates obtained 12 years apart, but from foods produced in a single facility (as well as associated human cases) indicated that an *L. monocytogenes* strain persisted in this plant for 12 years without any detectable genetic changes in the core genome.[253]

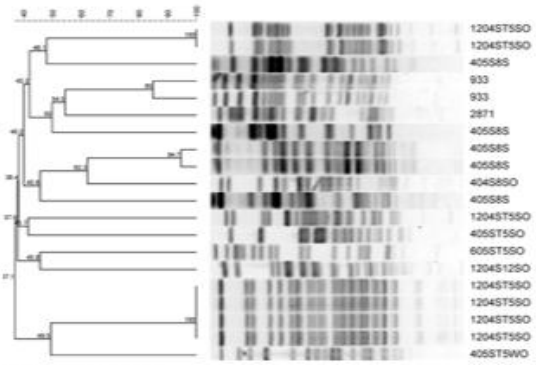

Figure: 5

Representative PFGE fragment patterns and dendrogram analysis of potentially pathogenic antimicrobial-resistant E. coli stains from urban watershed impacted by different sources of pollutants.

This suggests that *L. monocytogenes* transfer from one location (e.g., a farm) to at least one other location (e.g., processing plant, retail environment) may lead to a situation where isolates from different potential outbreak sources may show virtually identical genomes that may complicate trace-back. This also illustrates the need for good epidemiological data to facilitate appropriate interpretation of WGS data. As the WGS revolution in food safety has started to gain momentum, it is essential for everyone involved in food safety to understand both the basics of this technology as well as its already existing and future applications and uses. While this article will provide an introduction to the application of WGS in food safety, this field is constantly changing and new technologies are rapidly being developed and improved. It is therefore essential for food safety professionals to ensure that they continue to stay informed on advances in this field, which will have significant impact in food safety and beyond (e.g., food spoilage, food authenticity and fraud detection).

Whole-Genome Sequencing

The Basics While traditional sequencing methods have been used to sequence the complete genomes of bacteria, these methods are too time consuming and expensive to allow for routine use of bacterial WGS (figure 5) as part of surveillance systems or for bacterial characterization and subtyping. As described in detail in a number of review articles.[254,255]

The development and commercial introduction of new rapid-sequencing methods (often referred to as "next-generation sequencing" methods) have made it possible to perform routine WGS of bacterial isolates at costs and turnaround times that make these tools competitive with more traditional molecular subtyping methods. Development of these new genome-sequencing methods was initially driven by the desire to develop tools for sequencing of a complete human genome for less than $1,000. As bacterial genomes are roughly 1,000 times smaller than the human genome (the human genome contains about 3 billion base pairs, while the L. monocytogenes genome contains almost exactly 3 million base pairs), it is easy to see how development of tools to sequence a human genome for less than $1,000 will also yield tools that facilitate affordable bacterial genome sequencing. There are several commercially available platforms for bacterial genome sequencing that allow one to complete the actual sequencing of a bacterial genome for less than $50/isolate and with turnaround times, starting from a single bacterial colony, of fewer than 5 days. Typically, to achieve sequencing at costs under $50/isolate, a considerable number of isolates must be sequenced at the same time on a given instrument to achieve maximum economy of scale.

WGS of a single or a few isolates typically is an order of magnitude more expensive. This is important, as it means that in-house sequencing, for example, by a food company or food testing lab, will only be cost effective if large numbers of isolates are sequenced at the same time. Practically, this may mean longer turnaround times, as labs that receive few isolates may need to batch them into a single run and therefore may wait until they have accumulated enough isolates for WGS to be cost effective. With the current status of WGS, in-house sequencing capabilities are likely to be cost effective only if large numbers of isolates are being sequenced, or if sequencing equipment is used for multiple applications (e.g., WGS of pathogens, starter cultures and spoilage organisms and metagenomic sequencing). On the other hand, public health laboratories involved in foodborne disease surveillance typically will receive enough isolates to make WGS cost effective, particularly since WGS for different pathogens can be performed in the same run (unlike methods like PFGE, where different gels may be needed for different pathogens).

Advantages of WGS over Other Molecular Sub-typing Methods.

While PFGE (as well as other molecular methods) has had tremendous positive impacts on food safety, it and other methods have shortcomings and challenges that can and will, be overcome by WGS. For example, PFGE and other methods have shown limited discriminatory ability for some highly clonal pathogen populations, such as specific Salmonella serovars (e.g., Enteritidis[256] and Montevideo.[257] As WGS provides significantly improved subtype discrimination and can discriminate isolates that share identical PFGE types, WGS improves outbreak detection. For example, more than 50 percent of *Salmonella Enteritidis* isolates show identical PFGE types, but WGS can further differentiate isolates that share this common PFGE type and t(HUS) identify outbreaks that would not be detected by PFGE alone or even a combination of PFGE and MLVA.[256] PFGE also sometimes yields different patterns for isolates that are closely related. This occurs because a large part of bacterial genomes can rapidly change through

acquisition or loss of plasmids or chromosome-integrated prophages; typically, these types of changes yield isolates that differ by three or fewer bands in their PFGE patterns with a given enzyme. This can cause practical challenges: for example, when pathogen isolates from human patients and a food epidemiologically implicated as an outbreak source differ by one to three bands in PFGE. These types of findings complicate high-confidence assignment of an outbreak source. WGS, on the other hand, can easily and rapidly determine whether isolates that differ by specific genetic elements or by a few bands in PFGE are otherwise genetically closely related or not, as shown in the use of WGS to clarify the genetic relatedness of isolates in a large listeriosis outbreak that occurred in Canada in 2008.[258] Generally, WGS allows for highly improved discriminatory power as well as characterization of evolutionary relatedness of isolates, which is not possible with PFGE. In addition, WGS has technical advantages over PFGE and many other subtyping methods (figure 6). such as the potential for a higher level of automation, a simpler integrated work flow, reduced time of analysis and generation of highly standardized and compatible data even with different sequencing platforms.

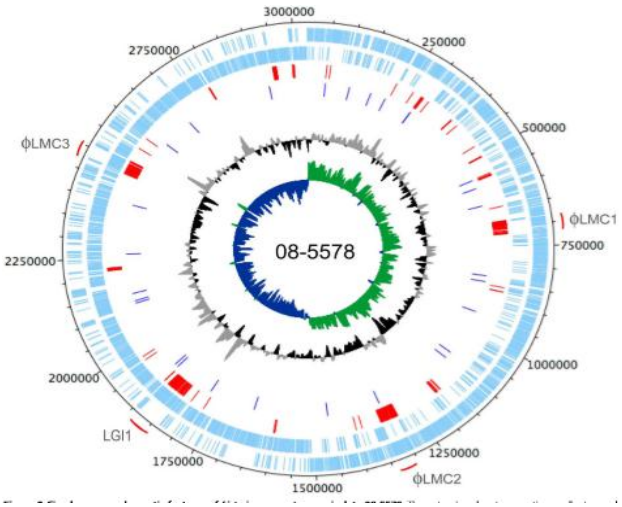

Figure 6: ***Circular map and genetic features of Listeria monocytogenes isolate 08-5578. The outer ring denotes genetic coordinates, and prophage and the novel 50 kbp Listeria genomic island (LGI1) are indicated in grey text. Prophage jLMC1 is not encoded within isolate 085923. Light blue bars (2nd and 3rd rings) denote coding sequences on the positive and negative strands, respectively. Red bars (4th ring) denote those coding sequences present in 08-5578 but absent in the genome sequence of strain EGDe. Dark blue bars (5th ring) indicate confirmed single nucleotide polymorphisms between isolate 08-5578 and 08-5923. The black/grey and blue/green plots indicate G+C content and G+C skew, respectively***

While rapid analysis of WGS data still remains somewhat of a challenge and may in some situations represent a bottleneck, easy-to-use, high-throughput bioinformatics tools for bacterial WGS data. Currently, reliable WGS data analysis still requires a trained bioinformatician to select, properly run and maintain the necessary pipeline of different analysis tools. Typical bioinformatics pipelines (Genomics, 2010) can now provide for initial WGS-based classification of isolates in less than 1 hour after raw data are downloaded from the actual sequencing hardware. Alternative approaches, such as a whole-genome MLST approach, which is currently used by the U.S. Centers for Disease Control and Prevention (CDC), further simplify analyses and allow for initial data analyses in a matter of minutes (e.g., 5 minutes as communicated in a CDC presentation).[259] These initial WGS data analyses do not provide detailed genomic information, such as identification of specific genes or prophages or plasmids, though; detailed and more lengthy data analyses are required to gain this type of additional information, which can provide valuable data on the genomic content of isolates, such as presenceof novel antibiotic resistance or virulence genes. Even there, rapid tools to extract and identify specific genes are being developed to allow for rapid identification of specific genomic elements and genes, such as antibiotic-resistance genes.[260,261]

Use of WGS for Foodborne Disease Surveillance With its advantages and rapidly decreasing costs, WGS has been integrated into routine foodborne disease surveillance. While retrospective studies on the use of WGS for foodborne disease surveillance have been conducted since about 2010, routine use of WGS was initiated by the CDC in 2013. Specifically, all L. monocytogenes isolates obtained from human disease cases in the U.S. have been characterized by WGS since fall of 2013.[262] Capabilities to perform WGS for this type of surveillance exist at some state public health laboratories as well as at CDC; the impact of WGS implementation has been seen with detection of a number of smaller listeriosis outbreaks.[263] At least some of which would have likely gone undetected with sole use of traditional subtyping methods such as PFGE. As it is being implemented in not just the U.S., WGS also will facilitate detection of multi-country outbreaks, as supported by exchange of L. monocytogenes genome sequences between CDC and Canadian investigators, which showed a perfect match between the genome sequences for a let isolate obtained in Canada and a human isolate obtained in Ohio.[264] While L. monocytogenes is a highly suitable model for initial implementation of WGS-based foodborne disease surveillance, due to both a relatively small number of human isolates per year and to its relatively small and easy-to-sequence genome, WGS also is increasingly used by public health and regulatory agencies to characterize other foodborne pathogens, in particular Salmonella. Importantly, U.S. government laboratories are moving to open release of isolate WGS data in real time, in Genome Trakr, even though metadata are still embargoed for a time. This will facilitate improved utilization of WGS data created for foodborne disease surveillance by groups other than public health laboratories.

WGS can also used for Source Trace-Back

In addition to routine WGS of human clinical isolates, routine WGS characterization of foodborne pathogen isolates obtained from food and environmental samples collected by regulatory agencies is increasingly common and has been spearheaded by the U.S. Food and Drug Administration (FDA). At this point, it is probably appropriate for the food industry to assume that any isolate obtained from a food or environmental sample collected by FDA undergoes characterization by WGS with subsequent comparison of the genome sequence to available human clinical isolates. This approach has started to lead to the identification of human cases and outbreaks likely linked to a contaminated food. For example, in 2014, genome sequences of L. monocytogenes isolated from recalled Hispanic-style cheese produced by Oasis Brands Inc. were found to be highly related to sequences of L. monocytogenes isolated from five ill people, one each in Georgia, New York and Texas and two in Tennessee; all of these individuals reported consuming Hispanic-style soft cheese, suggesting that these illnesses could have been related to products from Oasis Brands.[265] Importantly, however, WGS is not a magic bullet that allows for accurate and reliable identification of outbreaks and outbreak sources in the absence of appropriate food consumption history and epidemiological data. Continued investment in epidemiological data collection and analysis capabilities is critical to take full advantage of WGS-based subtyping data for foodborne pathogens.

The Future of WGS in Food Safety

The use of WGS-based characterization of foodborne pathogens by both public health and regulatory agencies will likely expand very quickly and may replace PFGE in the not-too-distant future. The technologies for WGS will also continue to develop and become increasingly simple, with a highly streamlined work flow that will facilitate more widespread application of these tools. With the rapid development of genome-sequencing technologies, food safety applications of sequencing beyond WGS will also rapidly grow. For example, metagenomic applications may have a major impact on food safety, particularly since these tools will allow for detection and identification of nonculturable and previously unknown pathogens, including bacteria, viruses and parasites, in both food specimens and clinical samples. With estimates that around 80 percent of foodborne disease cases in the U.S. are caused by unspecified agents, including known agents not yet recognized as causing foodborne illness, substances known to be in food but of unproven pathogenicity and unknown agents.[266] These tools likely will reveal the identity of some of these agents, which will provide opportunities to further reduce foodborne illnesses. Analysis of short-read metagenomics data may not always provide for accurate identification of bacteria present, though, and may provide potentially misleading data. For example, short DNA pieces from a nonpathogen could be misidentified as representing pathogen DNA[267], some of these issues will likely be overcome with new platforms that sequence larger DNA fragments. Industry adoption of WGS and metagenomic approaches for the detection and characterization of foodborne pathogens and disease agents may be slow and hampered by liability concerns. In addition to the potential for misidentification, metagenomics-based approaches may detect and sequence DNA from dead organisms, which are expected in any foods that undergo kill steps such as heat treatment. This may lead to false positives and associated misleading results when DNA from dead pathogens is detected in a properly processed and safe product. A key challenge will be to create a regulatory environment that will facilitate broad industry use of WGS, which will help ensure widespread application of these tools and consequently improve food safety, due to improved trace-back to contamination sources, for example. In the future, integration of WGS and other genomics-based tools with other large datasets (big data) will likely drive a big data paradigm shift in food safety, which has the potential for even larger food safety improvements.[268]

CONCLUSION

We all have a role to contribute in food safety. Food producers, processors and consumers can use techniques such as hand washing and proper labelling and sterilization of equipment to reduce the spread of harmful organisms. But genomics provides the forensics tools we need to fully understand how a given outbreak started, knowledge that is crucial to learning from our mistakes and preventing future outbreaks. They also offer insight in the underlying reasons why one strain is more harmful and virulent than another? and can point the way toward new vaccines, new antibiotics and other new strategies - such as probiotics, medicinal plant extract and green metal nanoparticles to fight against bacterial infections. In this way, genomics can help everyone enjoy safer food.

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