

# Current pathogenic *Escherichia coli* foodborne outbreak cases and therapy development

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**Abstract** Food contamination by pathogenic microorganisms has been a serious public health problem and a cause of huge economic losses worldwide. Foodborne pathogenic *Escherichia coli* (*E. coli*) contamination, such as that with *E. coli* O157 and O104, is very common, even in developed countries. Bacterial contamination may occur during any of the steps in the farm-to-table continuum from environmental, animal, or human sources and cause foodborne illness. To understand the causes of the foodborne outbreaks by *E. coli* and food-contamination prevention measures, we collected and investigated the past 10 years' worldwide reports of foodborne *E. coli* contamination cases. In the first half of this review article, we introduce the infection and symptoms of five major foodborne diarrheagenic *E. coli* pathotypes: enteropathogenic *E. coli* (EPEC), Shiga

toxin-producing *E. coli*/enterohemorrhagic *E. coli* (STEC/EHEC), *Shigella*/enteroinvasive *E. coli* (EIEC), enteroaggregative *E. coli* (EAEC), and enterotoxigenic *E. coli* (ETEC). In the second half of this review article, we introduce the foodborne outbreak cases caused by *E. coli* in natural foods and food products. Finally, we discuss current developments that can be applied to control and prevent bacterial food contamination.

**Keywords** Foodborne illness · *Escherichia coli* · Outbreak · Food contamination

## Introduction

*Escherichia coli* (*E. coli*) naturally form part of the normal flora in the gut of humans and other animals. In fact, most *E. coli* are considered harmless to humans (Croxen and Finlay 2010). However, certain pathogenic *E. coli* strains can infect the gut area and cause severe illness (Croxen et al. 2013). Pathogenic *E. coli* infection usually causes severe diarrhea. Diarrhea is the result of the reversal of the normal net absorptive status of water and electrolyte absorption to secretion. Worldwide, there are nearly 1.7 billion cases of diarrheal disease every year. Diarrheal disease is the second leading cause of death in children under 5 years old. Every year about 760,000 children under 5 years old die due to diarrheal diseases (Chowdhury et al. 2015). Fortunately, diarrheal disease caused by pathogenic *E. coli* is preventable by improved environmental sanitation and is treatable by antibiotics. The treatment of diarrheal disease is generally effective with oral rehydration and maintaining electrolyte balance through the diet. Patients with severe dehydration may require intravenous rehydration and use of antidiarrheal, pain relief drugs and antibiotics can slow

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down the patient's symptoms (Croxen et al. 2013). However, certain strains that can cause infections and illness become resistant to antibiotics (Collignon 2009; Tadesse et al. 2012). The pathogenic *E. coli* can be found in soil and water, usually as a result of animal fecal contamination (McAuley et al. 2014). Several pathotypes of *E. coli* have been reported and cause infectious diseases in humans (Table 1). Unsafe food also poses major economic risks, especially in a globalized world. According to the WHO website, the *E. coli* O104:H4 outbreak caused a loss of US\$1.3 billion to Germany's farmers and industries and required payments of US\$236 million in emergency aid to 22 European Union member states in 2011 (<http://www.who.int/mediacentre/news/releases/2015/food-safety/en/>). Clearly, pathogenic *E. coli* foodborne outbreak is still a significant cause of human illness worldwide.

### Pathogenic *E. coli*

Based on virulence factors, patterns of bacterial attachment to host cells, effects of attachment on host cells, production of toxins, and invasiveness, we will introduce the five major foodborne diarrheagenic *E. coli* pathotypes: enteropathogenic *E. coli* (EPEC), Shiga toxin-producing *E. coli* enterohemorrhagic *E. coli* (STEC/EHEC), *Shigella*/enteroinvasive *E. coli* (EIEC), enteroaggregative *E. coli* (EAEC), and enterotoxigenic *E. coli* (ETEC) (Table 2).

### Enteropathogenic *E. coli* (EPEC)

Enteropathogenic *Escherichia coli* (EPEC) are important diarrheal pathogens in children. In 1945, the EPEC strains were the first diarrheagenic *E. coli* to be identified during the outbreaks of infantile diarrhea in the United Kingdom (Bray 1945). In 1955, the term "EPEC" was first used by Neter (Neter et al. 1955). EPEC are highly prevalent in community settings (such as schools and hospitals) and are a main cause of persistent diarrhea (Hao et al. 2012; Park et al. 2014). The most common symptoms of EPEC illness are watery diarrhea, abdominal pain, nausea, vomiting, and fever. In addition to humans, EPEC can also infect animals such as cattle, dogs, cats, and rabbits (He et al. 2015; Singh et al. 2015). The infectious dose of EPEC in healthy adults has been estimated to be  $10^8$  organisms (Croxen et al. 2013). In most cases, EPEC-induced diarrhea is self-limiting and can be effectively treated with oral rehydration therapy. Persistent infections may require the use of antimicrobials. However, resistance to various agents has been reported (Langendorf et al. 2015; Malvi et al. 2015). In the past, diagnosis of EPEC was based on O:H serotype identification. In recent years, since the infection mechanism of

**Table 1** Characteristics of the foodborne pathogenic *E. coli*

Pathotype	Host(s)	Infectious dose (cfu)	Clinical symptoms	Main virulence factors/gene	Virulence associated plasmid	Site of colonization
EPEC	Children <5 year, adults at high inocula	$10^8$ – $10^{10}$	Watery diarrhea, vomiting, fever, abdominal pain and nausea	LEE, Intimin ( <i>eae</i> <sup>+</sup> ), BFP ( <i>bfp</i> <sup>+/-</sup> )	pEAF	Small intestine
STEC/EHEC	Adults, children	<1000	Watery diarrhea, HC and HUS	hemolysin ( <i>hly</i> ), <i>eae</i> <sup>+/-</sup> , <i>stx</i> <sup>+</sup> , <i>ehxA</i> <sup>+</sup>	pO157 encoding toxins	Distal ileum, colon
EIEC/ <i>Shigella</i>	Children <5 year, adults, immunocompromised persons, travelers	EIEC: $10^6$ – $10^8$ <i>Shigella</i> : 10–100	Shigellosis/bacillary dysentery, watery diarrhea, potential HUS	ShET1, ShET2, <i>ial</i> <sup>+</sup> , <i>ipaA</i> , <i>B</i> , <i>C</i> , <i>D</i> , <i>H</i> <sup>+</sup> , <i>stx</i> <sup>+</sup> ( <i>S. dysenteriae</i> )	Virulence/invasion plasmid (pINV)	Colon
EAEC	Adults, children in developing countries, travelers	$10^{10}$	Persistent diarrhea, HUS,	ShET1, ShET2, Pet, <i>aggR</i> <sup>+</sup> , AAF/I ( <i>aggA</i> <sup>+</sup> ) AAF/II ( <i>agg3A</i> ), AAF/III ( <i>agg3A</i> ), AAF/IV ( <i>agg4A</i> ), AAF/V ( <i>agg5A</i> ) EAST1( <i>astA</i> <sup>+</sup> ), dispersin ( <i>aap</i> <sup>+</sup> )	pAA encoding adherence factors and toxins	Small intestine, colon
ETEC	Children <5 year, adults, immunocompromised persons, travelers	$10^8$	Watery diarrhea	CFs, LT, ST	Plasmids encoding colonization factors and toxins	Small intestine

**Table 2** Selected major foodborne outbreaks caused by pathogenic *E. coli* during 2006–2015

Pathogen	Source	Date/duration	Country	Number of case	Serotypes	References
EPEC	Egg soup and tuna bibimbap	2013/05	South Korea	33	aEPEC O157:H45	(Park et al. 2014)
	Dining room	2010/09/16	China	112 (18–23 years old)	aEPEC O127a:K63	(Hao et al. 2012)
STEC/EHEC	Chipotle Mexican Grill restaurant	2015/10/19–2015/11/26	USA	55 (From 11 states)	O26	(CDC 2016)
	Costco Rotisserie Chicken salad	2015/11/03	USA	19 (From 7 states)	O157:H7	(CDC 2015)
	Raw clover sprouts	2014/05/1–2014/05/20	USA	19 (From 6 states)	O121	(CDC 2014a)
	Ground beef	2014/04/22–2014/05/02	USA	12 (1.8 million pounds of ground beef were recalled)	O157:H7	(CDC 2014b)
	Romaine lettuce	2011/10/10–2011/11/04	USA	58 (from 9 states)	O157:H7	(CDC 2012)
	Sprouts	2011/05/26–2011/06/16	USA	6 (4 HUS, 1 death)	O104:H4	(CDC 2011)
	Sprouts	2011/05/01–2011/07/04	German	3816 (810 HUS, 54 deaths)	O104:H4	(Buchholz et al. 2011; Frank et al. 2011)
	Fenugreek seeds	2011/06/08–2011/06/24	France	24 (7 HUS)	O104:H4	(King et al. 2012)
	Frozen ground beef products	2011/06/06–2011/07/15	France	18 (Children aged 6 months to 10 years old)	Sorbitol-fermenting <i>E. coli</i> O157:[H7]	(King et al. 2014)
	Raw beef dishes	2011/04–2011/05	Japan	181	O111 and O157	(Watahiki et al. 2014)
	Raw leeks and potatoes	2010/12–2011/07	England, Wales and Scotland	252 (1 Death)	O157 PT8	(Launders et al. 2016)
	Raw prepackaged cookie dough	2009/06/30	USA	72 (From 30 states)	O157:H7	(CDC 2009)
	Restaurant	2008/08/15	USA	341 (1 Death)	O111:NM	(Bradley et al. 2012)
Prepackaged spinach	2006/09/13	USA	205 (3 Deaths), involving 26 states	O157:H7	(CDC 2006; Jay et al. 2007)	
EIEC/ <i>Shigella</i>	Canteen (cooked vegetables)	2012/04/14	Italy	109	O96:H19 ( <i>ipaH</i> <sup>+</sup> )	(Escher et al. 2014)
	Unknown	2014/04/15–2014/06/13	American Samoa	280	<i>Shigella flexneri</i> serotype 7	(Painter et al. 2015)
	Suspected to cooked food and ice block	2013/09	Papua New Guinea	About 1200 (5 deaths)	<i>Shigella flexneri</i> serotype 2	(Benny et al. 2014)
	Bridge club	2012/05	USA	43	<i>Shigella sonnei</i>	(Sjolund Karlsson et al. 2013)
	Basil pesto	2011/10	Norway	46	<i>Shigella sonnei</i>	(Guzman-Herrador et al. 2013)
	Food on religious place	2010/02/11	India	About 150	<i>Shigella sonnei</i>	(Nandy et al. 2011)
	Canteen (food handler)	2009/11/13	Belgium	52	<i>Shigella sonnei</i>	(Gutierrez Garitano et al. 2011)
	Water	2009/06/05–2009/06/25	China	118	<i>Shigella flexneri</i> 2b	(He et al. 2012)

**Table 2** continued

Pathogen	Source	Date/duration	Country	Number of case	Serotypes	References
ETEC	Food on wedding party	2009/02/01	India	>300 (2–70 years old)	<i>Shigella sonnei</i>	(Nandy et al. 2011)
	Cold meat (school)	2006/09/01–2006/09/10	China	937	<i>Shigella sonnei</i>	(Xiao et al. 2012)
	Imported chives and scrambled eggs	2012/12/04–2012/12/09	Norway	>300	O78 (LT1 positive)	(MacDonald et al. 2015)
	Japanese restaurant	2012/09/15–2012/09/21	Japan	102	O169:H41	(Harada et al. 2013)
	Kimchi	2012	Korea	230 (from 7 schools)	O169	(Cho et al. 2014)
	Lettuce	2010/01/18–2010/01/20	Denmark	264	ETEC O6:K15:H16 and Norovirus	(Ethelberg et al. 2010)
	Fresh basil	2006/11	Denmark	About 200	ETEC O92:H- and O153:H2	(Pakalniskiene et al. 2009)
EAEC	Food festival (multi-pathogen)	2013/03	England	592	O131:H27, O104:H4, O20:H19	(Dallman et al. 2014)
	Cheese (unsterilized raw milk)	2006/02/20 and 2006/03/03	Italy	125	O92:H33	(Scavia et al. 2008)

EPEC has been well studied, diagnosis of EPEC will consider not only the serotypes but also consider phenotypes and genotypes (Araujo et al. 2007). EPEC contain a 35 kb cluster of virulence genes on the chromosomal pathogenicity island (PAI) called the locus of enterocyte effacement (LEE), which is necessary for virulence. EPEC are further classified into typical EPEC (tEPEC) and atypical EPEC (aEPEC). tEPEC harbor the *E. coli* adherence factor plasmid (pEAF). aEPEC contain the LEE but not the pEAF (Nakhjavani et al. 2013).

A hallmark phenotype of EPEC is the ability to produce attaching and effacing (A/E) lesions on the surfaces of intestinal epithelial cells. The colonization and fitness virulence factors produced by EPEC include intimin, bundle-forming pilus (BFP), Paa, and long polar fimbriae (LPF). Intimin protein is encoded by the *eae* gene on the chromosome that causes attachment and effacing lesions. BFP is encoded by the *bfp* gene on pEAF. BFP is a type IV pilus called the bundle-forming pilus that mediates interbacterial adherence and possibly adherence to epithelial cells (Martinez de la Pena et al. 2015). Due to the production of BFP, EPEC are capable of forming microcolonies and adhering to small-bowel enterocytes. Virulence factors of EPEC are translocated to the epithelial cells via the type III secretion system. Finally, cytoskeletons of the epithelial cells are derangements and are accompanied by an inflammatory response and diarrhea. In general, EPEC are noninvasive organisms and do not produce heat-labile (LT) or heat-stable (ST) enterotoxins.

EPEC belong to a group of pathogenic bacteria capable of causing A/E lesions on the surface of the host's intestinal epithelium.

### Shiga-toxin-producing *E. coli* (STEC)

*Escherichia coli* carrying the *stx* gene to produce Shiga toxins (Stxs) are defined as Shiga-toxin-producing *E. coli* (STEC), also known as verocytotoxin-producing *E. coli* (VTEC). Strains of STEC can cause hemorrhagic colitis (HC) and are commonly referred to as enterohaemorrhagic *E. coli* (EHEC) (Kaper et al. 2004). Transmission of STEC infection mainly occurs through eating or handling contaminated food and coming into contact with infected animals. Further person-to-person transmission is possible by close contact such as within families or at schools and in nursing homes (Busani et al. 2006). STEC can grow over a broad temperature range and in acidic conditions (Chaucheyras-Durand et al. 2010). STEC infections are mostly foodborne, and a variety of food sources such as undercooked ground beef, raw milk, salad, raw leeks and potatoes, vegetables, fruits, and other foods are implicated in outbreaks (Feng, 2014; Herman et al. 2015) (Table 2). The number of STEC required to cause human infection is low. In contaminated food, the presence of fewer than 1000 bacteria can cause human infection (Ahn et al. 2008; Karmali 2009). The symptoms of STEC infection in humans are watery

diarrhea, HC, hemolytic uremic syndrome (HUS), fever, abdominal cramping, and vomiting. General treatment is oral rehydration therapy and antibiotic therapy.

There are many serotypes of STEC such as O26, O111, O121, and O157 in which serotype O157:H7 is most often implicated in foodborne-illness outbreaks in the world. STEC O157:H7 has evolved step by step from non-toxigenic sorbitol-fermenting EPEC O55:H7. O55:H7 received the Stxs gene (*stx1* or *stx2*), large virulence-associated plasmid (pO157) and lost ferment sorbitol ability, and then changed to form the O157:H7 strain (Pennington 2010). STEC is often LEE positive and forms similar attachment and effacing lesions as EPEC. The main virulence factors of STEC are Stx, intimin, translocated intimin receptor (Tir), type III secretion system (T3SS), and hemolysin (*hly*) operon, which is encoded on the pO157 (Saitoh et al. 2008).

Stxs are exotoxin displays with an AB<sub>5</sub>-toxin structure containing an enzymatic A subunit non-covalently associated with five B subunits and only produced by STEC and *S. dysenteriae* serotype 1. The A subunit is a cytotoxic protein that can inhibit protein synthesis and damage the cells by apoptosis (Yang et al. 2015). The B subunit pentamer directs the binding form of the holotoxin on the eukaryotic cell surface; then the transportation “active” A subunit of the cell triggers the cell apoptosis process (Pacheco and Sperandio 2012). In addition to Stxs, most STEC carry a 92 kb pO157, which encodes a number of virulence factors such as hemolysin, adhesin (ToxB), periplasmic catalase-peroxidase (KatP), EspP to secrete serine protease, and type II secretion system. Due to a lack of transfer genes (*tra* and *trb*), pO157 cannot transfer by conjugation (Lim et al. 2010; Rump et al. 2012).

### ***Shigella*/enteroinvasive *E. coli* (EIEC)**

Enteroinvasive *E. coli* (EIEC) and *Shigella* strains have the ability to invade the human mucosa of the colon, M cells, macrophages, and the epithelial cells. EIEC is closely related to *Shigella* spp. and causes bacillary dysentery (also called shigellosis) in humans. Serotype classification can distinguish between EIEC and *Shigella*. In phylogenetic studies, housekeeping gene sequencing indicates that *Shigella* is more related to EIEC than to non-invasive *E. coli*. It is currently thought that *Shigella* is evolved from EIEC (Peng et al. 2009; van den Beld and Reubsæet 2012).

According to the O-antigen pattern, EIEC are classified into 21 major subtypes, and few EIEC have the H antigen (Croxen et al. 2013). *Shigella* are further classified as four species: *S. dysenteriae* (serogroup A, consisting of 15 serotypes), *S. flexneri* (serogroup B, consisting of 6 serotypes)

with 15 subtypes), *S. boydii* (serogroup C, consisting of 18 serotypes), and *S. sonnei* (serogroup D) (Niyogi 2005). In *Shigella* spp., only *S. dysenteriae* have the *stx* gene and secrete Stx to cause colitis and hemolytic uremia. In addition to Stx, *Shigella* can also produce endotoxins (ShET-1 and ShET-2) and virulence factors. The virulence plasmid is a ~220 kb large plasmid, and it encodes 50–60 virulence-associated genes on the *ipa-mxi-spa* region in *Shigella*. The virulence factors and endotoxins are transported into the host cell and cause infection via T3SS. As a result of infection, colonic cells are damaged and exhibit impaired absorption of water and nutrients, leading to watery diarrhea accompanied by blood and mucus in stools. Like *Shigella*, EIEC also carry a high molecular weight virulence plasmid (pINV) for invasion of the host and to destroy colonic tissue (Johnson and Nolan 2009). *Shigella* is highly virulent and has highly contagious organisms; a mere 10–100 organisms can cause diarrhea in healthy adults (Yang et al. 2015). Unlike *Shigella*, EIEC have a lower infection capability and require a higher number of organisms ( $10^6$ – $10^{10}$ ) to infect humans than *Shigella* (Hsia et al. 1993; Hsu et al. 2010).

The symptoms of *Shigella*/EIEC infection range from mild watery diarrhea to severe inflammatory bacillary dysentery characterized by strong abdominal cramps, fever, chills, and stools containing blood and mucus. Severe symptoms can even be fatal and severe life-threatening complications, including megacolon, intestinal perforation, peritonitis, pneumonia, and HUS, can occur (Schroeder and Hilbi 2008).

### **Enteroaggregative *E. coli* (EAEC)**

Enteroaggregative *E. coli* (EAEC), first identified in 1987, were defined by their bricklike aggregative patterns of adherence to cultured HEP-2 cells (Nataro et al. 1987). EAEC strains are important causative agents of traveler’s diarrhea and cause persistent diarrhea in immunocompromised children in developing countries (Okhuysen and Dupont 2010). EAEC harbor a ~110 kb aggregative adherence plasmid (pAA) that encodes virulence factor aggregative adherence fimbriae I (AAF/I; *aggA*), aggregative adherence fimbria II (AAF/II; *aafA*), aggregative adherence fimbria III (AAF/III; *agg3A*), and aggregative adherence fimbria IV (AAF/IV; *agg4A*), aggregative adherence fimbria V (AAF/V; *agg5A*), plasmid-encoded toxin (Pet), enteroaggregative heat stable toxin 1 (EAST1; *astA*), dispersin (*aap*), transcriptional activator AggR (*aggR*) regulon, and enterotoxin ShET2 (Aslani et al. 2011; Chaudhuri et al. 2010; Jonsson et al. 2015). The *aggR* regulon controls a number of EAEC virulence factor genes that code in the pAA and pathogenicity islands in the chromosome. Pet

shows enterotoxic activity and can degrade the cytoskeletal protein  $\alpha$ -fodrin and cleavage of the cytoskeletal protein spectrin to cause epithelial-cell rounding. EAST1 is a 38 amino acid peptide homologue of the ETEC STa toxin and could contribute to watery diarrhea in EAST1-positive strains (Kaper et al. 2004; Navarro-Garcia and Elias 2011). Dispersin is a colonization factor of EAEC and can promote EAEC dispersion across the intestinal mucosa (Sheikh et al. 2002). Some EAEC strains carrying with *stx* gene were called Stx-producing EAEC, such as O104:H4, O111:21, O111:H2 and O86:HNM strains were isolated from infected human (Buchholz et al. 2011; Dallman et al. 2012; Iyoda et al. 2000; King et al. 2012; Morabito et al. 1998).

The invasion process of EAEC can be divided into three steps. At first, AAF is expressed by EAEC and lets EAEC colonize the intestinal mucosa. Then, EAEC will produce a mucus-mediated biofilm on the enterocyte surface. Finally, the toxins are released from EAEC, causing the inflammatory response, intestinal secretion, and mucosal toxicity (Pereira et al. 2008). The symptoms of EAEC infection are often watery diarrhea with mucus and are accompanied by fever, vomiting, and abdominal pain. The EAEC infection treatments are oral rehydration therapy and antimicrobial therapy. Antibiotics are useful for treating cases of traveler's diarrhea. However, antibiotic resistance of EAEC is increasing worldwide (Aslani et al. 2011; Hill and Beeching 2010).

### Enterotoxigenic *E. coli* (ETEC)

In developing countries and semitropical areas such as Latin America, the Caribbean, southern Asia, and Africa, Enterotoxigenic *E. coli* (ETEC) are a major cause of traveler's diarrhea and the childhood diarrhea pathogen (de la Cabada and Dupont 2011). In developed countries, ETEC diarrhea is rare, although occasional outbreaks have been reported in Norway, Denmark, Japan, and Korea (Cho et al. 2014; Ethelberg et al. 2010; Harada et al. 2013; MacDonald et al. 2015). ETEC will produce fibrillar colonization factors (CFs) such as colonization factor antigen (CFA), coli surface antigen (CS), or putative colonization factor (PCF) to colonize in the small intestine. After adherence to small-bowel enterocytes, ETEC produces one or two enterotoxins, a heat-labile enterotoxin (LT), and a heat-stable enterotoxin (ST) (Jobling and Holmes 2012). LT and ST will be secreted out of *E. coli* and binding on the cell surface, then giving rise to intestinal secretion and causing diarrhea (Croxen et al. 2013). These CFs and enterotoxins LT/ST are often virulence plasmid encoded such as F18, K88 and K99

plasmids (Shepard et al. 2012). LT is an 86 kDa protein that assembles as an AB<sub>5</sub>-toxin. The structure and function are closely related to cholera enterotoxin (CT). LT causes diarrheal disease by deregulating host adenylate cyclase and also enhances ETEC adherence to intestinal epithelial cells (Johnson et al. 2009; Wang et al. 2012). In contrast, ST is a 2 kDa small single-peptide toxin that is nonimmunogenic in its natural form. ST activates guanylyl cyclase C and leads to an increase in the level of cGMP. In turn, cGMP mediates an increase in bicarbonate and chloride ion secretion and inhibition of sodium and chloride ion absorption, resulting in watery diarrhea (Taxt et al. 2010).

The typical clinical symptoms of ETEC infection are often watery diarrhea, abdominal pain, nausea, vomiting, and fever (Harada et al. 2013). The symptoms will last about 3–5 days. ETEC infection is acquired by ingestion of contaminated food or water (Taneja et al. 2011). The infective dose of ETEC for adults is estimated to be  $10^8$  organisms. However, children and the elderly may experience infection by lower organism numbers. Due to the high infectious dose, ETEC are spread by contaminated food and water, not by human-to-human transmission. Oral rehydration therapy and antibiotic therapy are very effective for ETEC infection diarrhea. In recent years, many reports have indicated that antimicrobial resistant ETEC strains are increasing worldwide (Do et al. 2006; Kalantar et al. 2013; Ochoa et al. 2009).

### Foodborne outbreak cases by pathogenic *E. coli* over the past 10 years

Bacterial contamination may occur during any of the steps in the farm-to-table continuum from environmental, animal, or human sources and cause foodborne illness. In the past 20 years, foodborne-illness outbreaks and cases associated with fresh produce have rapidly increased (Olaimat and Holley 2012). In the United States, leafy-vegetable-associated outbreaks have been larger than outbreaks associated with other food types. STEC were linked to 18% of leafy-vegetable-associated outbreaks between 1973 and 2012 (Herman et al. 2015). The cases of foodborne *E. coli* outbreaks associated with fresh vegetables and fruits numbered 46 and 7 from 2004 to 2012 in the United States and the European Union, respectively (Callejon et al. 2015). Food bacterial contamination caused not only human diseases but also serious economic damage. In the United States, foodborne illness costs the US economy about US\$10–83 billion each year (Nyachuba 2010). Foodborne-illness outbreak has also caused great economic losses in Europe and Australia

(McPherson et al. 2011; Toljander et al. 2012). To understand the causes of the foodborne outbreaks by *E. coli* and measures to prevent the food-contamination problem, we collected the past 10 years' worldwide reports of foodborne *E. coli* outbreaks (Table 2).

Over the past 10 years, foodborne outbreaks were chiefly caused by EPEC, STEC/EHEC, EIEC/*Shigella*, ETEC, and EAEC. Bacterial contamination may occur during any of the steps of the farm-to-table continuum. Contaminated foods can be divided into fruits and vegetables such as raw clover sprouts, romaine lettuce, sprouts, cucumbers, raw leeks and potatoes, spinach, basil pesto, lettuce and fresh basil; meat and meat products such as chicken salad, ground beef, raw beef dishes, raw pre-packaged cookie dough, chives and scrambled eggs, kimchi and cheese; and cooked food (due to the food handler) such as egg soup and tuna bibimbap. Sources of pathogens may come from a contaminated environment (water and soil), animals, and humans. Most of these foodborne *E. coli* outbreak cases were attributed to the consumption of undercooked and contaminated food such as ground beef hamburger and salad (uncooked vegetables). Outbreaks were also attributed to food prepared in restaurants or catering facilities, and ill food workers were implicated as the source of contamination (Gutierrez Garitano et al. 2011; Hao et al. 2012; Nandy et al. 2011; Park et al. 2014). STEC and *Shigella* are the strains most likely to cause outbreaks. The serotypes of STEC O104:H4, O157 PT8, O111:NM, and *S. flexneri* serotype 2 in the outbreaks resulted in deaths (Benny et al. 2014; Frank et al. 2011; Jay et al. 2007; Launder et al. 2016); and also outbreaks due to other serotypes resulted in deaths.

Recently, the most serious foodborne outbreak occurred in Germany in 2011 as a result of STEC O104:H4 (Buchholz et al. 2011; Frank et al. 2011). This outbreak resulted in 3816 identified STEC infections and 54 deaths, of which 32 were HUS-associated deaths. HUS is considered a disease that affects primarily children. However, 852 (22% of the 3816 STEC infections) cases of HUS occurred, of which 89% were adults. The identified outbreak source was raw sprouts. In addition to Germany, another 15 countries in Europe and North America had STEC O104:H4 outbreak cases. In the United States, six confirmed cases of STEC O104:H4 infections were identified. In five of the six cases, the individuals had traveled to Germany during the German outbreak. Four HUS cases and one death were reported. In France, twenty-four cases were identified. Of these, 22 (92%) cases were adults, 7 (29%) cases developed HUS, 5 (21%) developed bloody diarrhea, and 12 (50%) developed diarrhea. Fenugreek seeds were the only sprout type with an independent association to illness in multivariable analysis (King et al. 2012).

## Multidrug-resistant *E. coli*: recent treatment and prevention strategies

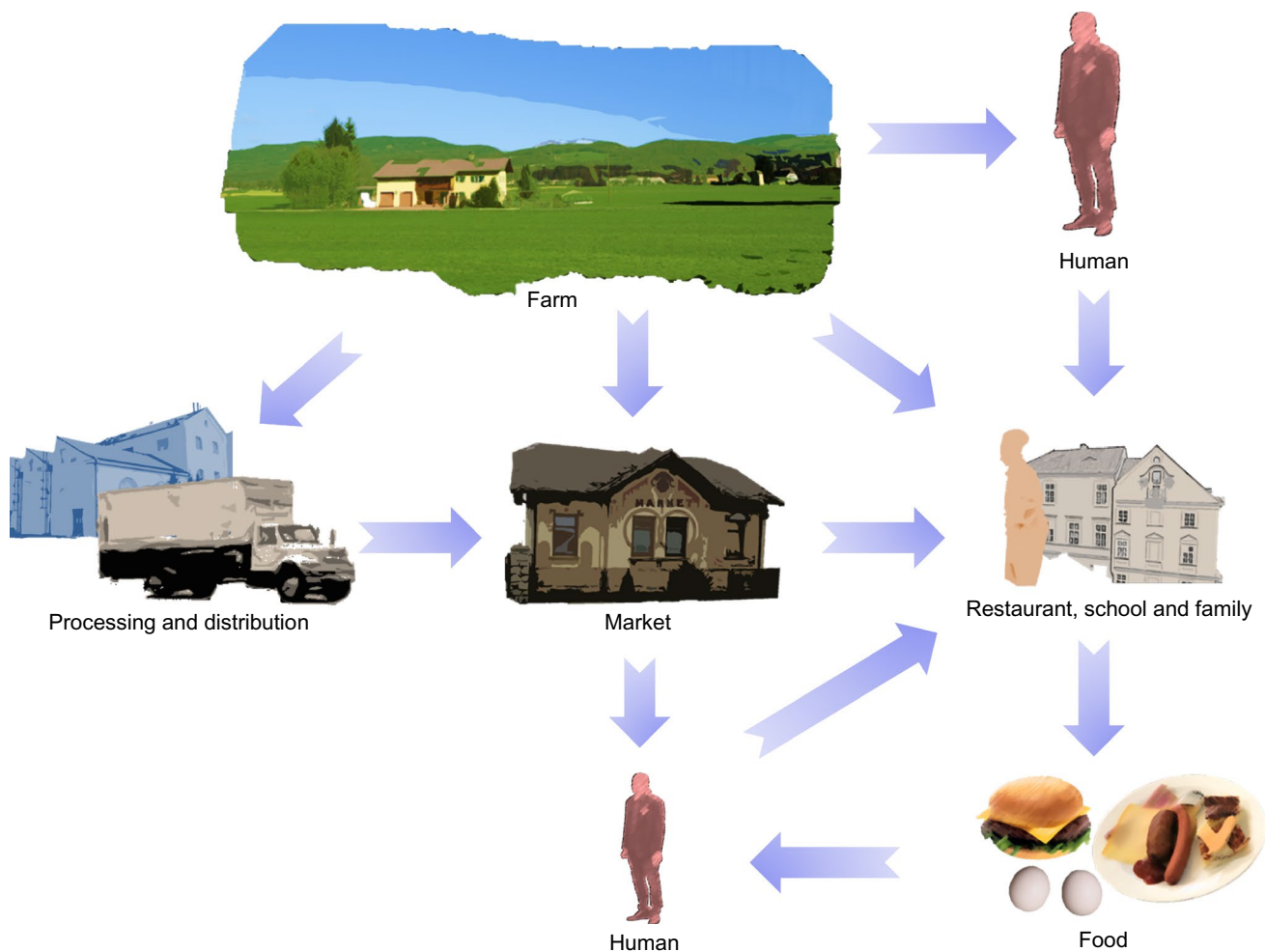
Food safety of fresh produce is a matter of increasing concern. Indeed, microbial contamination may occur during any of the steps in the farm-to-table continuum from environmental, animal, or human sources (Fig. 1). Therefore, the prevention and treatment of microbial contamination is one of the important food safety issues. In general, *E. coli* caused diarrheal disease is preventable by improved environmental sanitation and is treatable by oral or intravenous rehydration, antidiarrheal and antibiotics (Croxen et al. 2013). Here, we provide experimental treatment and prevention options that can be applied in food preservation and in the field of infectious diseases.

## Antibiotics

Antibiotics are efficient, powerful, and the most commonly used treatment against pathogenic *E. coli* in clinical and animal agriculture. However, large numbers of drug-resistant strains have appeared as the result of overuse of antibiotics in the past 50 years (Pasberg-Gauhl 2014). Antibiotics also kill the normal flora in intestinal tract and destruction the balance of intestinal microbial system (Langdon et al. 2016). Antibiotics such as ceftiofur and florfenicol used to treat animals have caused long-term persistence of ceftiofur/florfenicol-resistant *E. coli* found in animal feces and pen soils (Liu et al. 2016). Antibiotic treatment also brings an increased risk of the symptoms. Several antibiotics such as ampicillin cotrimoxazole, trimethoprim, azithromycin, and gentamicin for combating pathogenic *E. coli* have been shown to stimulate Stx release from *E. coli* (Grif et al. 1998; Mohsin et al. 2010). Despite this, antibiotics are still the main treatment used clinically against bacterial infections. New antibiotics with a new mode of action are urgently needed to combat resistant bacterial strains, but progress in developing them has been slow. Recently, an efficient screening method involving an antibacterial compound from soil microorganisms was developed (Ling et al. 2015).

## Antibodies

In addition to the use of antibiotics, antibody therapy is another method for neutralizing virulence factors and toxins from pathogenic *E. coli* and reducing symptoms (Cheng et al. 2013). However, face on bacterial diversity, the highly specificity of antibodies characteristic is also



**Fig. 1** Food supply chain and possible microbial contamination points. A typical foods supply chain is starting at the farm. The second stage is usually the processing and distribution to market. Retail stage the food products are purchased by restaurant, school or human. At last the foods are eaten by people. Microbial contamination may occur during any of the steps in the farm-to-table continuum from environmental, animal or human sources. The animal feces with path-

ogenic *E. coli* could contaminate water, soil and agricultural products. Pathogenic *E. coli* can transport by processing, distribution and retail stage. Finally, people are infected by eaten contaminated foods. The infected people such as cooks in the restaurant or school also can spread pathogens into the environment and foods that cause further outbreak

become one of the disadvantages of its application (Berry and Gaudet 2011; Casadevall 1996). Anti-Stx2 monoclonal antibodies were used to test the neutralization ability of Stx2 in vivo. Stx2 were injected into mice by iv and anti-Stx2 monoclonal antibodies were injected after 2 min. Anti-Stx2 monoclonal antibodies were shown to be capable of cleaning Stx2 completely from intoxicated mouse blood within minutes (Cheng et al. 2013). Antibodies also can be used to detect food contamination by STEC during the production process, thus reducing the risk of STEC outbreaks. The five high-affinity anti-Shiga toxin type 2 monoclonal antibodies (Stx2-1 to Stx2-5) were developed for in vitro tests and STEC detection in milk. Stx2-1 and Stx2-2 showed a high sensitivity to detecting Stx2a in milk (1 and 0.01 pg/mL). Stx2-5 was able to

neutralize Stx2a-mediated cytotoxicity in Vero cells (He et al. 2013). Combining antibiotic and antibody is a promising strategy for future STEC treatments. Skinner et al. (2015) demonstrated that combined tigecycline and Stx antibody can fully protect Vero cells from Stx toxicity and STEC O157:H7 infection (Skinner et al. 2015). The virulence factor fusion protein antibody can target different antigens and enhance neutralization activity. Stx2AI and *E. coli* secreted protein A (EspA) fusion protein antibody was reported to exhibit strong neutralization activity and protection capability against STEC O157:H7 in vitro and in vivo (Cheng et al. 2009). The anti-virulence factor antibody development could help improve detection of STEC in livestock, food, the environment, and in clinical samples, resulting in improved food safety and human health.



## Vaccines

Many studies have indicated the feasibility of *E. coli* vaccines. The *E. coli* vaccine development usually used attenuated *E. coli*, inactivated whole *E. coli*, virulence factors, and toxins to induce immune responses in humans. To date, numerous *E. coli* vaccines have been developed and reviewed (Walker 2015). The disadvantage of vaccines is that effective duration of the immunity is short. There is still no vaccine available to effectively control the spread of pathogens *E. coli* (Saeedi et al. 2017). Behrens (2014) developed a skin-patch vaccine containing the ETEC LT. In the phase 3 study, the vaccine efficacy was 34.6% in a population of travelers to Mexico and Guatemala. In addition, LT antigen was effectively delivered by the skin-patch, but the vaccine did not protect travelers against diarrhea caused by ETEC or other organisms (Behrens et al. 2014). The oral, live attenuated, three-strain recombinant bacterial vaccine, ACE527, was developed by the Darsley group. In the phase 2 study, ACE527 was demonstrated to generate strong immune responses to CFA and LT of ETEC in human volunteers (Darsley et al. 2012). The oral, live attenuated *Shigella dysenteriae* type-1 vaccine SC599 was developed by the Launay group. This *Shigella dysenteriae* 1 strain attenuated by deletion of invasion (*icsA*), iron chelation (*ent* and *fep*) and *stx* genes. In the phase 1 study, SC599 vaccine elicits a significant circulating IgA ASC and serum antibody response in volunteers and protects volunteers against shigellosis symptoms (Launay et al. 2009). The principle of the DNA vaccine is to encode the virulence factor gene in a plasmid for expression to stimulate the immune system to produce antibody and other immune responses. Recently, the anti-EHEC DNA-based vaccine was developed. The plasmid DNA (pVAX*efa-1'*) was carrying truncated EHEC factor for adherence-1 gene (*efa-1'*) and immunized C57BL/6 mice. Vaccinated mice can be detected with anti-EHEC-secreted protein antibodies and protected against challenge with *E. coli* O157:H7 strain EDL933 (Riquelme-Neira et al. 2016).

## Bacteriocins

Bacteriocins are natural, abundant, and highly diverse, and the genes encoded ribosomally are synthesized antimicrobial peptides (AMPs) or proteins produced by bacteria. For survival, bacteria will produce bacteriocins to reduce the number of competitors to obtain more nutrients and living space in environments. More than 99% of bacteria can produce at least one bacteriocin, most of which are not identified (Yang et al. 2014). Bacteriocins are also considered as basically safe food additives after intake by the gastrointestinal system (Perez et al. 2014). Bacteriocins are natural

food additives due to the bacteriocin-producing bacteria presence in many types of foods. Therefore, bacteriocin-producing bacteria or bacteriocins can be applied on the food against food-spoiling bacteria and food-borne pathogens. At present, only a few bacteriocins are allowed to be used in food or feed and are not treated as a therapeutic drug. On the other hand, the *E. coli* can obtain the different bacteriocin immunity genes by conjugation maybe causes the bacteriocin to be ineffective (Rankin et al. 2011).

Recent studies also have confirmed that bacteriocins can be applied to food preservation. A novel bacteriocin Paracin 1.7 is produced by *Lactobacillus paracasei* HD1-7, which is isolated from Chinese sauerkraut juice. Paracin 1.7 has heat stability (121 °C for 20 min) and characteristics of antimicrobial activities at a broad pH range (3.0–8.0). Paracin 1.7 also has a wide antibacterial spectrum against Gram positive (e.g., *Staphylococcus*, *Micrococcus*, *Bacillus*, and *Lactobacillus*) and Gram negative bacteria (e.g., *Proteus*, *Escherichia*, *Enterobacter*, *Pseudomonas*, and *Salmonella*) (Ge et al. 2009, 2016). Pattanayaiying et al (2015) combined the antimicrobial compound lauric arginate and nisin Z into pullulan films and applied them on the fresh or further-processed muscle foods. The antimicrobial pullulan films displayed excellent inhibition against the foodborne pathogens *E. coli* O157:H7, O111, and O26 on fresh and further-processed muscle foods (Pattanayaiying et al. 2015). Antimicrobial pullulan films can extend the shelf life of food products. Enterocin AS-48 was applied on soybean sprouts and apple juice against *E. coli* O157:H7 (Ananou et al. 2005; Cobo Molinos et al. 2008).

## Nature product

Foodborne pathogen contamination of food crops or livestock products may occur through the contamination of livestock feed by manure. Several studies indicate that a traditional and naturally medicinal plant can be applied in manure and animal feed to reduce the number of foodborne pathogens. However, the content of antimicrobial substances in natural herbs is very rare and must be further purified for drug development (Pan et al., 2013). Neem (*Azadirachta indica*) is a traditional medicinal plant in India, South Africa, and Southeast Asia. A 5% neem leaf and bark supplement content in manure can effectively reduce the number of the outbreak strain of *E. coli* O157:H7 (EHEC), but neem oil cannot (Ravva and Korn 2015). *E. coli* O157:H7 can be transported by the water source and cause contamination during the food-production process at dairies and feedlots. Adding the plant extract or drugs to the feed

and wastewater to enrich the protozoa (*Vorticella microstoma*) in cattle manure could be a strategy to control the environmental dissemination of *E. coli* O157:H7 from dairies to produce-production environments (Ravva et al. 2013). Darwish and Aburjai studied the anti-multidrug-resistant *E. coli* activity of 19 Jordanian plants. It was shown that the combination of plant material and antibiotic could improve the antibiotic activity against multidrug-resistant *E. coli* (Darwish and Aburjai 2010). Cheese contamination with foodborne bacterial pathogens could happen from diverse sources during cheese production or storage. The plant extracts used in cheese may serve as antibacterial agents against serious foodborne pathogens such as *E. coli* O157:H7 *Listeria monocytogenes*, *Salmonella* Typhimurium, and *Staphylococcus aureus*. In cheese, adding the *Cinnamomum cassia* bark extract can inhibit the growth of *E. coli* O157:H7; the food minimal inhibitory concentration is 300 µg/mL. Plant extract additives not only act as potential natural and safe antimicrobial alternatives but also as spices and flavoring agents to improve the texture of cheese (Tayel et al. 2015). The application of inexpensive antibacterial plant supplements in greater quantities to control pathogens in manure and possibly in produce fields may be an option for controlling the transfer of foodborne pathogens from farm to fork.

## Bacteriophages

Bacteriophages (phage) are bacterial viruses (viruses that infect bacteria) that can be found in all natural environments such as animal feces, waste water, and soil. In animal agriculture, phages can be applied to control diseases caused by pathogenic *E. coli* (Zhang et al. 2015). Numerous phages were isolated and reported to act against pathogenic *E. coli*. The phage has highly specificity on against the bacteria and which is the disadvantage for the treatment of different types of bacterial infections (Loc-Carrillo and Abedon, 2011). Jamalludeen et al. (2007) reported that nine phages were isolated in sewage from pig farms. These phages show lytic activity against O149:H10:F4 and O149:H43:F4 ETEC strains that caused porcine post-weaning diarrhea (Jamalludeen et al. 2007). Recently, a novel lytic coliphage JS09, which was isolated from sewage samples of a swine farm in China, was reported. JS09 could infect clinically isolated antibiotic-resistant avian pathogenic *E. coli* and ETEC in vitro (Zhou et al. 2015). These results also confirmed that phage can be applied in the environment to control the pathogenic *E. coli* population. A phage cocktail can be applied on food to reduce *E. coli* contamination and increase food safety. Three lytic phages, e11/2, e4/1c, and

pp01, were mixed as a cocktail and applied on the beef's surface that was contaminated with a rifampin-resistant *E. coli* O157:H7 human strain. The result showed that seven of the nine beef samples had no *E. coli* O157:H7 contamination (O'Flynn et al. 2004). This indicates that the surface application of phages is a feasible approach for food preservation and could also be applied to other meats. A phage cocktail also can be applied on humans. A 9-phage cocktail was tested on healthy adult volunteers at a high oral dose of  $3 \times 10^9$  and at a low oral dose of  $3 \times 10^7$  plaque-forming units and placebo, respectively. The 9-phage cocktail was seen to have no impact with fecal microbiota composition from stool, and no adverse effects were observed on liver, kidney, and blood functions (Sarker et al. 2012). Bacteriophage receptor binding proteins (RBPs) can help phage to recognize specific receptors on the bacteria surface and achieve infection. Due to specific binding to bacteria as antibody characteristics, RBPs may be applied against *E. coli* (Simpson et al. 2016).

## Other treatments

Other ways to treat or prevent *E. coli* contamination, such as probiotics, antimicrobial nanoparticles, and radiation treatment, had been reported. In daily food, continuous-supply probiotics could help humans and livestock to face pathogenic microorganisms. Probiotics can secrete anti-bacterial or anti-virulent agents to act against pathogenic *E. coli*. *Lactobacillus acidophilus* La5 was incorporated into yogurt. The anti-virulent agents from *Lactobacillus acidophilus* La5 could downregulate *stxB2*, *qseA*, *luxS*, *tir*, *ler*, *eaeA*, and *hlyB* virulence gene expression of EHEC (Zeinhom et al. 2012). X-ray radiation treatment could be applied to the surface of food. X-ray radiation treatment effectively reduced *E. coli* O157:H7, *S. flexneri*, and other foodborne pathogens to less than 100 cfu on whole Roma tomatoes (Mahmoud 2010). In recent years, antimicrobial nanoparticle technology was developed and studied to determine treatments against drug-resistant microorganisms. Treatments included use of silver nanoparticles, zinc oxide nanoparticles, and cationic surfactant nanoparticles (Hwang et al. 2014; Morsy et al. 2014; Paredes et al. 2014). Cationic surfactant nanoparticles have positively charged properties and could kill bacteria by (1) disruption of bacteria cell wall/membrane and affecting membrane permeability; (2) generate free radical and ROS; (3) interaction with proteins affecting their correct function (Yang et al. 2016). Antimicrobial nanoparticles could be applied on vacuum-packaged meat and poultry products to control the foodborne pathogens *E. coli* O157:H7 (Morsy et al. 2014).

## Conclusion

Most *E. coli*—associated foodborne outbreak cases over the past decade have been attributed to the consumption of uncooked foods contaminated by pathogenic *E. coli* at source and during the preparation process. Pathogenic *E. coli* not only caused huge economic losses as a result of these cases but also impacted human health and even caused death. There have been many studies to develop novel antimicrobial drugs and vaccines against pathogenic *E. coli* and disease symptoms. However, drug therapy and antimicrobial substances applied to the environment and food are only a temporary solution. The quality improvement of environmental sanitation and personal hygiene may be the best way to prevent pathogenic *E. coli* infection and foodborne outbreak (Mara et al. 2010).

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