Gut Pathogens

REVIEW

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Overview of pathogenic *Escherichia coli*, with a focus on Shiga toxin-producing serotypes, global outbreaks (1982–2024) and food safety criteria

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Abstract

Classification of pathogenic *E. coli* has been focused either in mammalian host or infection site, which offers limited resolution. This review presents a comprehensive framework for classifying all *E. coli* branches within a single, unifying figure. This approach integrates established methods based on virulence factors, serotypes and clinical syndromes, offering a more nuanced and informative perspective on *E. coli* pathogenicity. The presence of the LEE island in pathogenic *E. coli* is a key genetic marker differentiating EHEC from STEC strains. The coexistence of *stx* and *eae* genes within the bacterial genome is a primary characteristic used to distinguish STEC from other pathogenic *E. coli* strains. The presence of the *inv* plasmid, Afa/Dr adhesins, CFA-CS-LT-ST and EAST1 are key distinguishing features for identifying pathogenic *E. coli* strains belonging to EIEC, DAEC, ETEC and EAEC pathotypes respectively. Food microbiological criteria differentiate pathogenic *E. coli* in food matrices. 'Zero-tolerance' applies to most ready-to-eat (RTE) foods due to high illness risk. Non-RTE foods' roles may allow limited *E. coli* presence, which expose consumers to potential risk; particularly from the concerning Shiga toxin-producing *E. coli* (STEC) strains, which can lead to life-threatening complications in humans, including haemolytic uremic syndrome (HUS) and even death in susceptible individuals. These findings suggest that decision-makers should consider incorporating the separate detection of STEC serotypes into food microbiological criteria, in addition to existing enumeration methods. Contamination of STEC is mainly linked to food consumption, therefore, outbreaks of *E. coli* STEC has been reviewed here and showed a link also to water as a potential contamination route. Since their discovery in 1982, over 39,787 STEC cases associated with 1,343 outbreaks have been documented. The majority of these outbreaks occurred in the Americas, followed by Europe, Asia and Africa. The most common serotypes identified among the outbreaks were O157, the 'Big Six' (O26, O45, O103, O111, O121, and O145), and other serotypes such as O55, O80, O101, O104, O116, O165, O174 and O183. This review provides valuable insights into the most prevalent serotypes implicated in STEC outbreaks and identifies gaps in microbiological criteria, particularly for *E. coli* non-O157 and non-Big Six serotypes.

Keywords *Escherichia coli*, STEC, O157, Big Six, Food poisoning, Epidemiology, Outbreaks, SFDA and Microbiological Criteria

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Introduction

Escherichia, a genus of anaerobic gram-negative bacilli, belongs to the family Enterobacteriaceae [1]. In 1884, a German paediatrician named Theodore Escherichia was the first to isolate *E. coli* from the faeces of human infants [2]. Later, *E. coli* was found to colonize the intestinal tract of infants just after birth, within few hours [3]. Usually, *E. coli* strains coexist with humans, conferring benefits and rarely causing disease, except in immunocompromised individuals [3]. However, some *E. coli* strains have acquired virulence factors, which allow them to cause various diseases [3]. The transfer of these virulence factors between strains results a novel combination within the genomes of different strains. In general, pathogenic strains of *E. coli* cause three different illnesses in humans, namely: urinary tract infections (UTIs), enteric/diarrhoeal disease and sepsis/meningitis [3]. *E. coli* strains also infect animals. Examples include avian pathogenic *E. coli* (APEC), which result respiratory infections, septicaemia and pericarditis in poultry [4]; mammary pathogenic *E. coli* (MPEC), which causes mastitis in cattle [5]; and endometrial pathogenic *E. coli* (EnPEC), which targets the endometrium in cattle (derived from the extra-intestinal pathogenic *E. coli* [ExPEC] group, Fig. 1) [6]. *E. coli* belonging to the intestinal pathogenic *E. coli* (IPEC) group (Fig. 1) also contains several serotypes that infect animals, including rabbit entero-pathogenic *E. coli* (REPEC), dog entero-pathogenic *E. coli* (DEPEC) and porcine-enteropathogenic *E. coli* (PEPEC) [7]. The present review discusses only pathogenic *E. coli* that causes intestinal disease in humans.

General classification of *E. coli*

There are hundreds of *E. coli* strains, including somatic (O) '173 strains', capsular (K) '80 strains', flagellar (H) '56 strains' and fimbrial (F) 'unknown strains', which are serologically classified based on surface antigens [8, 9]. There are 160 pathotypes involved in hospital-acquired pneumonia (HAP), surgical site infections (SSI), inflammation of the meninges, gastrointestinal tract infections, haemolytic uremic syndrome (HUS) and UTIs [9]. To avoid confusion, it is important to note that HUS is classified into three types: typical HUS (tHUS), atypical HUS (aHUS) and secondary HUS. The first type, tHUS, is the result of *E. coli* O157 infection [10]. The second type, aHUS, is caused by various factors,

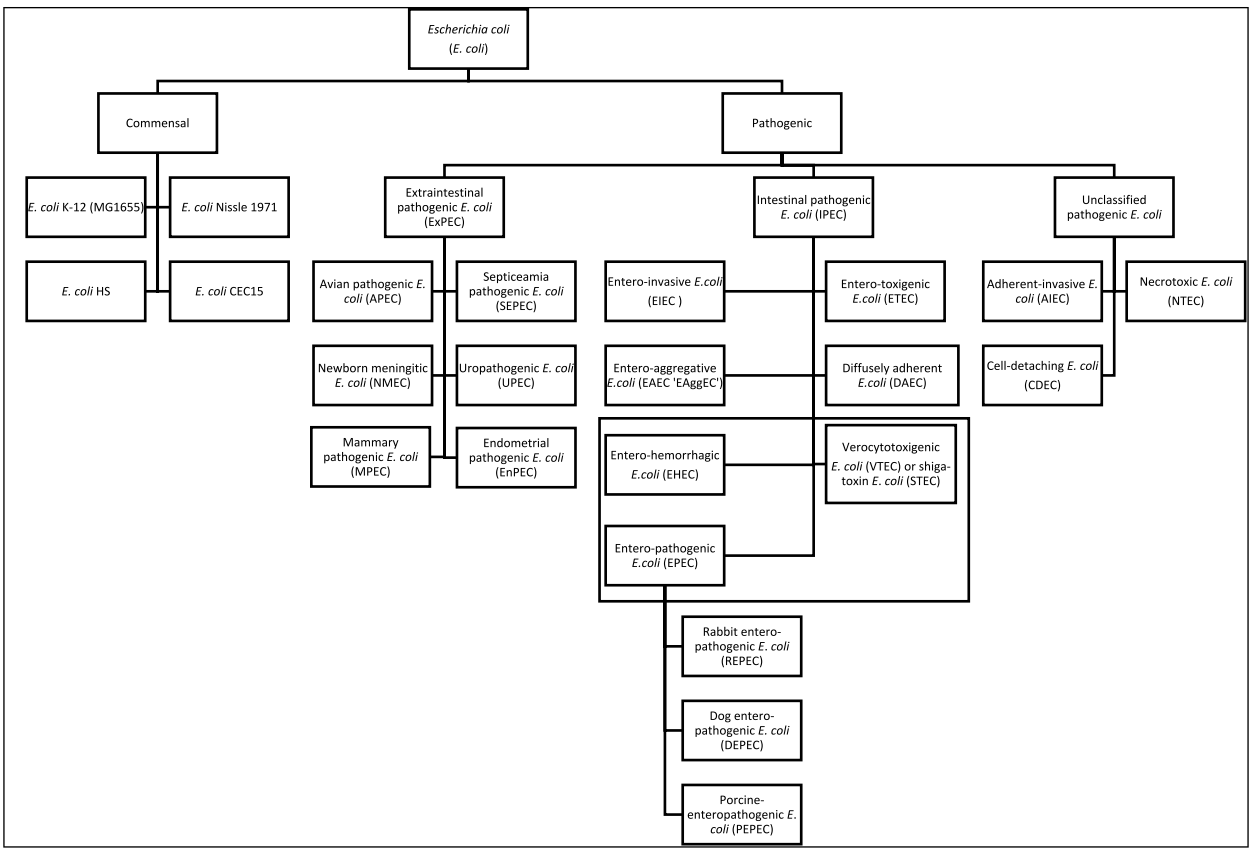


Fig. 1 Classification of commensal and pathogenic *E. coli*. The O157 strain can be derived from EHEC, VTEC'STEC' or EPEC, as indicated

such as mutations, autoantibodies, autoimmunity, transplantation, cancer, infection, certain cytotoxic drugs or pregnancy, which lead to dysregulated complement activation. Finally, secondary HUS is caused by *Streptococcus pneumoniae* and the influenza virus [10].

In this review, we present a comprehensive classification system of *E. coli* strains (Fig. 1). The most well-known commensal strains of *E. coli* are as follows: K-12, Nissle 1917, HS and CEC15 [11–13]. K-12 is the most commonly used host strain in gene cloning experiments because it has the following advantages: (i) genetically, it is the most well understood of *E. coli* strains; (ii) it is easily modified by many genetic methods, and (iii) it is classified as a biologically safe vehicle for the propagation of gene cloning and expression vectors in all major national and international guidelines on biological safety [14].

E. coli pathotypes can be distinguished into two main groups based on whether they cause infection inside (IPEC) or outside the gastrointestinal system (ExPEC) [8]. IPIC are also known as diarrheagenic *E. coli* [15]. There are three unclassified pathogenic groups: adherent-invasive *E. coli* (AIEC) involved in Crohn's disease (CD) [16–18], necrotoxic *E. coli* (NTEC) which is associated with humans and animals diseases and cell-detaching *E. coli* (CDEC) that involved in the haemolysin production [3].

Among ExPEC, there are six known pathotypes. Three of these mentioned earlier, namely, (i) APEC, (ii) MPEC and (iii) EnPEC, cause severe animal disease. The other three pathotypes, (iv) septicaemia pathogenic *E. coli* (SEPEC), (v) new-born meningitic *E. coli* (NMEC) and (vi) uropathogenic *E. coli* (UPEC), are involved in sepsis, new-born meningitis and UTIs, respectively [6, 19].

Among IPEC that contain shiga toxin (Stx)-producing *E. coli* (STEC), the bacilli strains are grouped genetically into the following pathotypes: (i) enteroinvasive *E. coli* (EIEC), which causes dysentery; (ii) enterotoxigenic *E. coli* (ETEC), which causes traveller's diarrhoea; (iii) enteroaggregative *E. coli* (EAEC) (also termed EAggEC), which causes persistent diarrhoea in humans; (iv) diffusely adherent *E. coli* (DAEC) which causes diarrhoea in children; (v) enterohaemorrhagic *E. coli* (EHEC), which causes haemorrhagic colitis (HC) and HUS; (vi) verocytotoxigenic *E. coli* (VTEC) newly termed STEC, a subclass of EHEC and the most widespread of these pathogens that causes severe HC in humans; and (vii) enteropathogenic *E. coli* (EPEC), characterized by the formation of 'attaching and effacing' (A/E) intestinal lesions [3], which causes diarrhoea in both animals and children (Fig. 2). Of note, EIEC and EAEC strains are found only in humans and not in animals [8].

STEC strains (O157 and the Big Six O26, O45, O103, O111, O121 and O145) according to serotype analysis

STEC was named due to its ability to produce verocytotoxin/Stx (VT/Stx) that targets vero cells of its host by disturbing protein synthesis [20]. The name Stx was used due to the similarity of the toxin produced by *Shigella dysenteriae* [15]. The Japanese microbiologist Kiyoshi Shiga (1870–1957) was the first to discover these toxins [30]. STEC belongs to the IPEC group, which contains various pathotypes, as described earlier. Figure 2 depicts the relationship between these pathotypes [20].

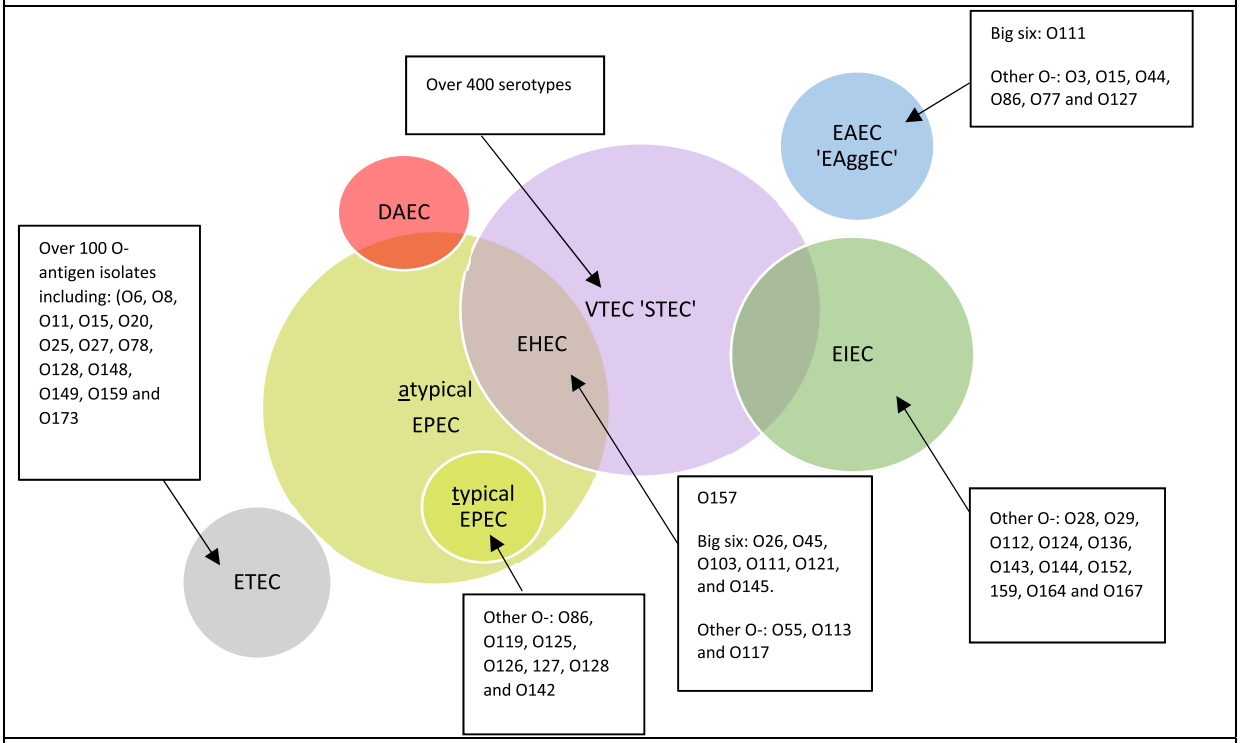
E. coli STEC/EHEC has over 400 serotypes. The serotype O157 is the most frequently isolated serovar from the STEC group (Fig. 2). Serovar O157 leads to serious diseases, such as HUS, HC in the humans gastrointestinal tract, due to the production of S*tx* [15].

Some *E. coli* serotypes, such as O26, can be classified into more than one serogroup, which can be under STEC or/and EPEC and is the most common big six (non-O157) strains that cause both HC and HUS (Fig. 2) [15]. EPEC can be typical (tEPEC) or atypical (aEPEC) and both possess a locus of enterocyte effacement (LEE), a pathogenicity island (PAI) that causes AE lesions. However, only tEPEC has an EPEC adherence factor (EAF) plasmid, which encodes bundle-forming pilus (BFP) encoded by the *bfpA* gene [15]. aEPEC normally expresses enteroaggregative *E. coli* heat-stable enterotoxin 1 (EAST1) encoded by the *astA* gene [15]. The LEE is discussed in the STEC pathogenicity section.

E. coli O111 is another big six serotype involved in human enteropathogenic and enterohaemorrhagic illnesses [23]. Due to its phenotypic and genetic diversity, O111 has been classified as EPEC, EHEC and EAEC. Variety of O111 strains has been investigated previously, Alharbi et al. (2022)'s review showed that a strain of O111 that expressed H2, H12 and H21 (flagella antigens) was isolated from children with diarrhoea; and another strains, that expressed H and H2 carried the EAF plasmid, which is a feature of EPEC [15]. However, EHEC O111 produces Stx is considered the most frequent strain responsible for bloody diarrhoea and HUS worldwide [15]. O111:NM (non-motile), O111:H2, O111:H8 and O111:H12 are linked to the enteropathogenic serogroup and classified as EHEC and EAEC [23].

EHEC O121 produces Stx and involves in HUS and HC [31]. Serogroups from the latter strain generally cause shigellosis-like sickness due to the presence of virulence factors similar to that found in *Shigella* [31]. Although the presence of EHEC virulence genes logically place the strain O121:H19 in the EHEC member group,

A



B

Pathotypes	Virulence factor								Symptoms	References
	VT/ST toxin (stx1, stx2<eae)	LEE	A/E lesion	EAF	220 kb (inv) plasmid	Afa/Dr adhesins	CFA and CS antigens and LT and STa an STb toxins	EAST1 (homologue of STa)		
VTEC"STEC"	✓								Bloody and mild diarrhea, HUS and TTP	[3,149]
EHEC	✓	✓	✓						Bloody diarrhea	[3]
tEPEC		✓	✓	✓					Bloody diarrhea, fever and vomiting	[15]
aEPEC		✓	✓					✓	Non-bloody diarrhea in infants and Bloody diarrhea in patients	[158]
EIEC					✓				Watery diarrhea	[3,29]
DAEC						✓			Infantile diarrhea	[3]
ETEC							✓		Watery diarrhea	[3]
EAEC"EAggEC"								✓	Acute diarrhea	[3]

Fig. 2 Classification of intestinal pathogenic *E. coli* (IPEC). **A** Venn diagram illustrating the relationship between IPEC pathotypes, adapted and modified from [20, 21]. **B** Virulence factors and symptoms of IPEC pathotypes [3, 22]. The strains in **A** were collected from studies sited here [15, 23–25]. *TTP: thrombotic thrombocytopaenic purpura. Afa: afimbrial adhesins are encoded by the *afa* gene clusters that responsible for the invasions process in the host cell [26]. Dr: Drori blood group antigen adhesins allow *E. coli* to invade the host epithelial *CD55* that encode complement decay-accelerating factor 'DAF' in human [26, 27]. CFA: colonization factor antigens (at least 23 member) are involved to facilitate *E. coli*' bacterial attachment to the host small intestines. CS: Coli surface antigens. ST/LT: heat stable (ST) and heat-labile (LT) are enterotoxins associated with diarrhoea. ST types (STa) and (STb) are involved with human and animal diarrhoea respectively [28]. EAF: plasmid of 70–100 kb called the EAF (EPEC adherence factor) [3]. 220 kb (inv) plasmid: 220 kb virulence-associated (inv) plasmid [29]. (✓) Normally exist (✓) sometimes exist

its sequence indicates that this strain does not belong to either EHEC or EPEC [15].

E. coli O45 is an interested serotype since it infects human and avian [32]. The STEC O45 causes a sporadic bloody diarrhoea in humans. The strain O45:H28 shares a common ancestor with five O157:H7 strains, including the *E. coli* Sakai strain (isolated originally in Japan) [15]. The avian pathogenic plasmid pS88 is the essential genetic element involved in the virulence of the APEC O45:K1:H7 [32].

The serotype O103 is an EPEC-like *E. coli* involved in rabbit enteritis (type: rhamnose-negative) and HUS in children [33, 34]. Since then, the STEC O103 serotype has been involved in a number of outbreaks, especially the strains O103:H2 and O103:H11 [15]. *E. coli* O103:H2 was ranked as the third most repeatedly isolated EHEC serotype between 1997 and 2000 in Germany [35].

STEC O145 is the last big six member described herein. It causes waterborne infections in humans and is an important cause of HUS and HC [36]. STEC O145 has many serogroups, O145:NM, O145:H28, O145:H25, O145:H34, O145:H8, O145:H16, and O145:HNT (non-typeable) [37].

Reservoir and transmission of STEC

Transmission of STECs to humans occurs through consumption of contaminated foods, such as raw or undercooked ground meat and raw vegetables or direct contact with an infected person [38]. Ruminants, particularly cattle, are the primary reservoirs of STEC worldwide. [39]. Moreover, STEC has been isolated from many environments, including drinking water sources [36]. In beef production, the meat production process has been identified as an area where STEC infection can be controlled and prevented [40]. The route of transmission of various STEC serotypes is shown in Fig. 3.

Food handling practices of food supply chain can contribute significantly to STEC transmission. In facilities where meat is processing, contaminated equipment, utensils or surfaces can cross-contaminate cuts of meat, especially ground (minced) beef which mixes trimmings from various parts or sources [41]. Moreover, inadequate temperature control during storage and transportation can allow various bacteria notably STEC to multiply [41, 42]. In retail shops, storing leaking pre-packaged meats next to raw products can create opportunities for cross-contamination [41]. Food delivery services, while convenient, may introduce another potential point of failure: improper temperature control during transport or contamination from delivery containers may facilitate STEC growth or transmission, which may introduce a risk to consumers [43]. These scenarios highlight the critical role of stringent hygiene protocols, preventing cross-contamination and controlling temperature at every stage of the food chain, and the latter steps are important to minimize the risk of STEC outbreaks associated with bad handling practices.

Pathogenicity and infection of STEC serotypes

Gene-encoding virulence factors are similar among STEC serotypes. However, the number/code assigned to individual STEC strains depends on the location of these virulence factors in plasmids, pathogenicity islands (PAIs) and other mobile elements. The the PAI LEE possesses several key pathogenic genes, such as the *eae* gene, which encodes intimin, as well as a type III secretion system and translocated intimin receptor. The gene *eae* is encoding A/E lesions and located on the LEE [44], which contributes to STEC pathogenesis by increasing bacterial attachment to intestinal epithelial cells [15]. The LEE and its contents are responsible for A/E lesions induced on host intestinal epithelial cells [39]. The presence of LEE is linked to HUS, at least in some STEC serotypes [15]. It is important to mention that, STEC harbouring-LEE is called EHEC [45]. STEC also has two *stx* genes, *stx1* and *stx2*, that produce the following subtypes: four (Stx1a, Stx1c, Stx1d and Stx1e) and 12 (Stx2a–Stx2l) respectively. STEC expresses Stx mainly when the phage becomes lytic during STEC lysis by the host [39]. A combination of *stx2a* and *eae* genes is linked to bloody diarrhoea and the development of HUS in infected individuals [15].

STEC pathogenicity is also linked to the presence of haemolysin virulence factors (*ehxA, hlyA, e-hlyA* and *sheA*). The *ehxA* factor is a plasmid-encoded enterohaemolysin and genetically grouped into six subtypes (A–F), which are involved directly in HUS and cases of diarrhoea. It is used as an epidemiological marker to detect STEC serotypes. Alpha-haemolysin (*hlyA*) is associated with UTI, produced by many strains. The role of the bacteriophage-carried enterohaemolysin (*e-hlyA*) is poorly understood. The presence of *sheA* has been confirmed in many STEC pathotypes. However, its function is still unknown [46].

The ability to accurately differentiate between STEC serotypes is crucial for effective outbreak investigations and prevention. As an example, to difference between O26 and O157, the chu and ybt genes (which encode for iron uptake systems) have been marked as potential discriminators between these two significant STEC serotypes. While O157 serotypes typically harbor chu genes for heme-mediated iron acquisition, O26 serotypes are more commonly associated with ybt genes that involved in siderophore-mediated iron uptake. This genetic distinction offers a molecular approach to classify O26 and O157, contributing to improved

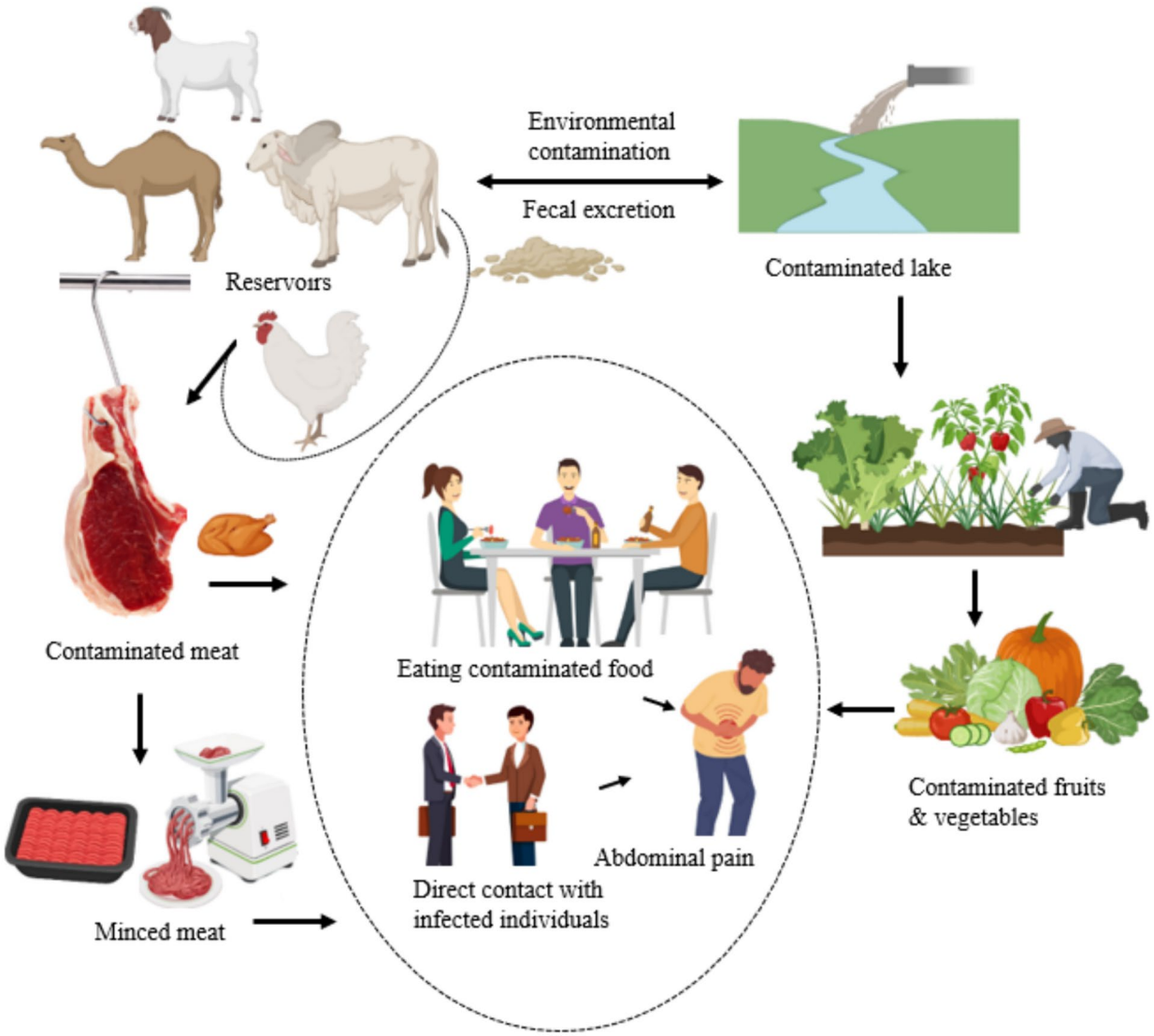


Fig. 3 Multiple routes of STEC transmission from different environment sources. (Created in BioRender.com)

epidemiological surveillance and public health response [47].

STEC outbreaks during 1982–2024 (to date)

An outbreak in microbiology is typically defined as a cluster of illnesses caused by a specific organism, exceeding the expected baseline for a particular area and timeframe [48]. A single-etiology outbreak is a term used to define an outbreak caused by one serotype, whereas, a multiple-etiology term is used to define an outbreak caused by one serotype with evidence of existing of another serotype [15].

Since 1982 and 1984, respectively, both O157 and non-O157 STEC have been implicated in outbreaks [49, 50]. Since then, over 1,343 outbreaks effecting more than 39,787 individuals across 4 continents and over 30 countries have been documented due to STEC serotypes infections (Table 1). According to Ota et al. (2019), the largest STEC outbreak ever recorded is occurred by O157 during 1996 in Sakai, Japan which effect approximately over 8000 individuals [51]. Based on our data, the second largest outbreak of STEC was caused by O104:H4 which effected over 4000 individuals, 22% of those developed HUS [52]. Most STEC outbreaks worldwide are caused by mainly consuming food specially meat and green leaves [15, 53]. Besides that, different serotypes of STEC show an ability to adapt in

Table 1 Summary of *E. coli* STEC recorded outbreaks worldwide during 1982–2024

#	Country	Years (covered	Organism	Number of outbreaks	Number of infected individuals	Source	References
1	USA	1982–2002	O157	350	8598	Food: ground beef and others Non-food: person to person, recreational water, animal contact, drinking water, laboratory-related	[54]
	USA	2003–2012[†]	O157	390	4928	Food: beef, poultry, dairy, leafy vegetable, fruits, sprouts, nuts and others Non-food: person-to-person, water and others	[55]
	USA	2010–2017[†]	O157	330	3353	Food: vegetables, row crops, beef, dairy, fruits and others Non-food: person-to-person, animal contact, water and others	[56]
	USA	1983–2002	O111 O104 O121 O103 O26	7	115	Food: milk, salad bar, Punch Non-food: lake water and day care	[57]
	USA	2003–2009	OUnd:H8 O45:NM O45:H2 O26:H11 O165:NM O121:H19 O111:NM O45 O111 O111:H8 O121:H19	21	584	Food: lettuce-based salad, blueberries, strawberries, barbecued pork and unpasteurized milk Non-food: goats and others	[58]
	USA	2010–2017	O26 O111 O121	124	1047	Food: vegetables, row crops, beef, dairy, fruits and others Non-food: person-to-person, animal contact, water and others	[56]
	USA	2018–2019	O157	2	234	Food: romaine lettuce	[59]
	USA	2019	O103	1	209	Food: ground beef	[15]
	USA	2023[‡]	O157	1	13	Non-food: Pressurized municipal irrigation water (UPMW)	[60]
	USA	2024[‡]	O157 +non-O157	1	25	Non-food: Swimming water	[61]
	USA	2024[‡]	O157:H7	1	5	Food: Store-made guacamole	[62]
2	Canada	1995–2018	O157	5	428*	Food iceberg lettuce, shredded lettuce, Leafy greens and romaine lettuce	[53, 63, 64]
	Canada	2016–2018	O121	3	42	Food: flour and raw milk	[65, 66]
	Canada	2023[‡]	O157:H7	1	250	Non-food: a central kitchen of a daycare centre	[67]
3	Argentina	2002–2009	O157:H7 O26:H11 O103:H2 O145:NM ONT:HNT O174:H21	12	56	Food: bovine meat and sausage Non-food: person-to-person, swimming pool and others	[68]
4	Brazil	2019	O157: H7	1	24	Non-food: in a day care centre	[69]

Table 1 (continued)

#	Country	Years (covered	Organism	Number of outbreaks	Number of infected individuals	Source	References
5	Germany	1988	O157	1	6	–	[50]
	Germany	2000	O26:H11	1	11	Food: bovine meat	[49]
	Germany	1995–1996	O157:H-	1	28	Food: sausages (beef)	[49]
	Germany	2009–2013	O157	2	25	Food: raw milk Non-food: tent camp, school, kindergarten and human-to-human	[70]
	Germany	1011–2014	O104:H4	2	Over 4000	Food: Fenugreek seeds sprouts Non-food: Food handler contamination	[15]
6	Denmark	2003	O157:H-	1	25	Food: organic caw milk	[49]
	Denmark	2007	O26	1	20	Food: beef sausages	[15]
7	Belgium	2007	O145 O26	–	12	Food: ice cream	[15]
	Belgium	2012	O157:H7	1	24	Food: bovine-derived products	[71]
8	Sweden	1999–2013	O157	3	200	Food: lettuce and salad	[53]
9	France	1995–2006	O157	3	710	Food: beef burger, bovine meat and raw milk cheese	[49]
	France	1996–2006	O26 O80 O111 O55	–	320	Food: bovine meat and caw cheese	[49]
	France	2011–2019	O104:H4 O26:H11	3	52	Food: raw cow's milk cheese and fenugreek sprouts	[72–74]
10	Slovakia	2003	O157	1	9	Food: unpasteurized cow milk	[49]
11	Russia	2013	O157:H7 +non-STEC O101:H33	1	–	Food: milk and mom specific food samples Non-food: clinical specimens	[75]
12	Italy	1992	O111	1	9	–	[49]
	Italy	2013	O26	1	15	Food: local milk-processing establishments	[76]
13	Romania	2016	O26	1	20	Food: local milk-processing establishments	[76]
14	Finland	1997–2013	O157:H7 OUnd	7	1067	Food: Hamburger, kebab and unpasteurized milk Non-food: swimming water and water (non-specific)	[77, 78]
	Finland	2016	ONT:H11 O111:H8	1	237	Food: rocket	[15, 77]
15	Netherlands	1995	O157	1	21	Food: steak tartare (raw beef)	[49]
	Netherlands	2005	O157	1	32	Food: steak tartare (raw bovine)	[49]
	Netherlands	2007	O157	–	50	Food: lettuce	[15, 49]
16	Iceland	2007	O157	1	35	Food: lettuce	[49]
17	UK[¶]	2013–2016	O157	6	369	Food: watercress, rocket, slaw and bagged mix salad	[53]
	UK[¶]	2002	O157:H7	1	15	Non-food: drinking water	[78]
	UK[¶]	2014–2018	O55:H7	1	46	Non-food: Animal-to-person	[79]
	UK[¶]	2023[‡]	O183:H18	1	24	Food: ground (minced) beef	[80, 81]
	UK[¶]	2024[‡]	O145	1	227	Food: salad leaves	[82]
18	Scotland	1990	O157:H7	1	492	Non-food: drinking water	[78]
	Scotland	1995	O157:H7	1	633	Non-food: drinking water	[78]
	Scotland	1999	O157:H7	1	6	Non-food: drinking water	[78]
	Scotland	2004	O157:H7	1	5	Non-food: drinking water	[78]
19	Wales	2002	O157:H7	1	16	Non-food: drinking water	[78]
20	Ireland	2005	O157	1	18	Non-food: person to person and water	[83]

Table 1 (continued)

#	Country	Years (covered	Organism	Number of outbreaks	Number of infected individuals	Source	References
21	Czech rep	1988	O26:H11 O157	1	5	Non-food: tap water	[50]
22	Japan	1984	O145:H-	1	100	–	[50]
	Japan	1986	O111:H-	1	23	–	[49]
	Japan	1990	O157:H7	1	174	Non-food: tap water supplied from the well in a school	[84]
	Japan	1991	O111:H- O?:H19	2	323	–	[50]
	Japan	1996	O157	1	8500	Food: radish sprouts	[53, 85]
	Japan	2011	O157 O111	1	181	Food: raw beef	[86]
23	China	1999	O157	16	372	Food: unknown Non-food: patient, cattle, chicken, goat and pig	[85, 87]
24	India	2002	O116	1	7**	–	[88]
25	South Korea	2013	O157:H45	1	33	Food: Egg soup and tuna bibimbap	[86]
26	Iran	2015	Non-157 +other *E. coli*	1	14	Non-food: waste contamination of drinking water	[89]
27	Australia	1995	O111:NM	1	158	Food: sausage	[15]
	Australia	2000–2010	O157 O111 O26	11	822	Food: unknown Non-food: Animal-to-person, person-to-person and water	[90]
28	Swaziland	1992	O157	1	>100	Food: linked to consuming beef and untreated water	[91]
29	Cameroon	1997	O157 +other non-*E. coli* pathogens	1	281	Food: pies (kanda) prepared with smoked zebu meat	[92]
30	South Africa	2017	O26: H11	1	4	Food: fruits, vegetables and dried beef meat products	[93]
Total			≤22	≤1343	≤39,787		

ǂ Recent outbreaks

Ŧ 2010, 2011 and 2012 USA data maybe overlapped, Ound, ONT and HNT: undetermined

*Number may not be accurate (refer to references)

**Effected are calves

NM non-motile, *USA* United States of America and *UK*Ŧ United Kingdom, which reflects outbreaks' data spread between England, Scotland, Wales and maybe Northern Ireland

Note: the data presented may underestimate the true burden of STEC outbreaks due to potential underreporting and variations in outbreak classification criteria across different years and countries. Countries by continent: 1–4: America (north and south), 5–21: Europe, 22–27: Asia and 28–30: Africa

other environments such as, water, person-to-person and animal contacts (Table 1).

Of the six STEC outbreaks recorded in 2023 and 2024 (Table 1, indicated by ǂ), two were attributed to contaminated water sources (Virginia and Utah incidents). which could be evidence suggesting that water is a likely a contamination route. These findings agree with Kintz et al. [53] who concluded that 4 out of 6 STEC strains identified in irrigation water were involved in multiple outbreaks between 1995 and 2018. This evidence highlights the growing concern of STEC transmission as a waterborne.

No official STEC outbreaks have been announced or published in 2022, however, the annual report of EU/EEA for 2022 confirmed that there were 8565 cases of STEC (2.5 cases per 100,000 population) with 25% increase in the case of incidents compared to 2021 report. From those incidents, 568 (6.3%) case developed HUS [94]. To explore STEC outbreaks reported prior to 2022, please refer to the following articles [15].

As indicated in Table 1, the United States has the highest recorded number of STEC outbreaks. This is likely attributable to the systematic tracking of incidents

through PulseNet, a Centers for Disease Control and Prevention (CDC) initiative established in 1996 [95].

In contrast to other continents listed in Table 1, only three STEC outbreaks have been recorded in Africa. This may indicate either a lower prevalence of STEC in the region or inadequate surveillance systems leading to underreporting. A comprehensive understanding of the situation requires further investigation to differentiate between these possibilities.

Antimicrobial resistance of STEC

The emergence of antimicrobial resistance in STEC is a concerning public health issue. Overuse and misuse of antibiotics in human contribute to the development of antibiotic resistance in bacteria including STEC. This resistance can limit the effectiveness of antibiotics, making it more challenging to treat infections caused by these bacteria. Although antibiotics are among the most effective drug treatments to be developed, the ability of bacteria to develop resistance to antibiotics became apparent soon after antibiotic use became widespread. For decades, the solution to this problem was to develop new antibiotics. However, this option has markedly declined in recent years due to an increase in the prevalence of antibiotic-resistant bacterial infections, which have a negative influence on human health [96].

Treating STEC infections with antimicrobial therapies has become a matter of debate because antibiotics may result in lysis of bacterial cell walls, resulting in the release of Stx toxins, which then enhance the expression of *stx* genes in vivo. However, HUS can still be prevented if antimicrobials are given in the early stages of infection [97].

Antibiotics are commonly used in animal production for disease prevention and growth promotion. However, these practices inevitably lead to the development of antibiotic resistance among commensal communities in animals' digestive systems, thereby posing a public health danger [98]. A recent and comprehensive study in Saudi Arabia tested a number of STEC serotypes isolated from carcasses against 14 commonly used antibiotics. 20 out of 110 STEC isolates (identified as, O26, O44, O111, O146 and O166) were 100% resistant to penicillin and 80% were resistant to erythromycin. Both are used effectively to treat livestock and improve their performance [99]. This finding is an alert for livestock stakeholders to understand and avoid such scenarios that can foster the emergence of resistance in their production system.

It is known that overuse of antibiotics in livestock production is a major concern for human health in developing countries [100].

The role of microbiological criteria around the world in controlling the presence of *E. coli* in food

Food microbiological criteria describe the acceptability of consuming food lots based on the prevalence of microorganisms therein (colonies' enumeration or detection) [101] and the presence of pathogens' toxins/metabolites per defined unit [101]. Microbiological criteria are classified into three groups: (i) standards, which are contained in laws and with which compliance is mandatory; (ii) specifications, which are applied to raw materials, ingredients or end products and normally included in purchase agreements; and (iii) guidelines, which are applied at different food stages (e.g. processing and retailing) that may involve varied microbiological conditions [102].

Twenty sets of microbiological criteria applied in at least 58 countries were collected for investigation (Table 2). We observed that some sets of criteria are applied mainly by one country, such as Canada, Brazil, Turkey, India, the Philippines, Indonesia, Thailand, China, Hong Kong, Japan, Singapore, South Korea and South Africa, while other sets of criteria are applied in unions of countries, such as in the European Union (EC No. 2073/2005) that may applied by 30 EEA (European Economic Area) countries [103], the 6 Gulf Cooperation Council (GCC) countries, namely Saudi Arabia, UAE, Kuwait, Bahrain, Qatar and Oman (GSO 1016/2015), [104] and Australia and New Zealand (Compendium of Microbiological Criteria for Food) [105]. It is worth noting that the UK besides applying EC No. 2073/2005 for approving food matrices for consumption; is applying the Guidelines for Assessing the Microbiological Safety of Ready-to-Eat Foods Placed on the Market (2009) published by the Health Protection Agency [106] and the Handbook of Microbiological Criteria for Foods (2020) published by the Institute of Food Science and Technology [107], for assessing food safety against microbes, this explanation was received after an enquiry emailed to the UK Health Security Agency. In Hong Kong, there is no set of microbiological criteria for raw meat, this information received from Food and Environmental Hygiene Department.

Of the twenty criteria sets listed in Table 2 , only thirteen include at least one type of carcass meat. The remaining seven criteria sets, which belong to Ireland, India, the Philippines, Indonesia, Thailand, Australia and New Zealand, do not include any type of carcass meat. However, all the sets of criteria included RTE, except for the one related to South Africa. We tried to find sets of criteria applied in a number of countries that are not mentioned in Table 2, but perhaps due to confidentiality considerations or a lack of written guidelines, we found no set of microbiological criteria applied in Iraq,

Table 2 Summary of existing testing of *E. coli* and *E. coli* STEC and/or O157 in microbiological criteria for meat and RTE food products

		Raw														RTE		Reference
		Carcass meat								Mechanically prepared meat (processed meat and non-specific)					Fishery products (non-specific)	Meat (non-specific)	Other products (does not include meat) α	
Region	Authority and/or Criteria code	Cattle (beef)	Sheep	Goat	Horse	Pig	Chicken	Turkey	Meat (non-specific)	Parts and/or steaks	Minced	Fermented	Sausages	Other (refer to reference				
America	USA	✓	–	–	–	–	–	–	–	✓	✓	✓	✓	–	–	–	✓	[108–112]
	Canada	✓	–	–	–	–	–	–	–	✓	✓	✓	✓	–	E	✓	✓	[113–117]
	Brazil	E	–	–	–	E	E	E	–	E	E	E	E	–	E	–	E	[118–120]
Europe[T]	(EC) No. 2073/2005	E	E	E	E	E	–	–	–	–	E	–	–	–	E	–	✓	[103]
	UK Ω	–	–	–	–	–	–	–	–	–	–	–	–	–	–	✓	✓	[106, 107]
	Scotland Ω	E	E	E	E	E	–	–	✓	–	E	–	E	–	–	–	–	[121]
	Ireland Ω	–	–	–	–	–	–	–	–	–	–	–	–	–	–	✓	E/✓	[122, 123]
	Turkey Ω	E	E	E	E	E	–	–	–	E/✓	E/✓	✓	✓	–	E	–	✓	[123, 124]

Table 2 (continued)

Region	Authority and/or Criteria code	Raw														RTE		Reference
		Carcass meat								Mechanically prepared meat (processed meat and non-specific)					Fishery products (non-specific)	Meat (non-specific)	Other products (does not include meat) α	
		Cattle (beef)	Sheep	Goat	Horse	Pig	Chicken	Turkey	Meat (non-specific)	Parts and/or steaks	Minced	Fermented	Sausages	Other (refer to reference				
Asia	India	–	–	–	–	–	–	–	–	E	E	E	E	–	E	–	✓	[125]
	Philippines	–	–	–	–	–	–	–	–	E	–	E	E	–	E	E	E	[124, 126]
	Indonesia	–	–	–	–	–	–	–	–	E	E	E	–	–	E	–	E	[127]
	Thailand	–	–	–	–	–	–	–	–	–	–	–	–	–	E	E	E	[128]
	China	✓	✓	–	–	–	✓	✓	✓	✓	–	✓	–	✓	E	✓	✓	[129, 130]
	Hong Kong	–	–	–	–	–	–	–	–	–	✓	–	–	–	E	E	✓	[131]
	Japan	E	–	–	–	–	–	–	–	E	E	E	E	E	E	E	E/✓	[131, 132]
	Singapore	✓	–	–	–	–	–	–	✓	E	E/✓	–	E/✓	E/✓	–	–	E/✓	[133–136]
	South Korea (Republic of Korea)	–	–	–	–	–	–	–	E	–	–	–	–	E	E	E	E	[137]
	Australia and New Zealand[‡]	–	–	–	–	–	–	–	–	–	✓	✓	–	–	–	–	✓	[105, 137–141]
	GSO 1016/2015[❖]	–	–	–	–	–	–	–	E/✓	–	E/✓	–	E/✓	–	E	–	✓	[104]
Africa	South Africa[♦]	E	E	E	E	E	–	–	E	✓	–	–	–	–	–	–	–	[142]

USA United States of America, *EC* Commission Regulation of European Commission (EC) No. 2073/2005, *UK* United Kingdom; a criterion tests the product against (✓) *E. coli* STEC and/or O157, (E) *E. coli* enumeration and (–): no requirements publicly available for the latter tests

[Ŧ] The EC No. 2073/2005 criteria are applied in European countries; however, some European countries have other food criteria indicated with Ω symbol

[‡] Compendium provided by Food Standards Australia New Zealand (FSANZ)

[❖] The GCC Standardization Organization (GSO) 1016/2015 criteria are applied in the GCC countries

[♦] This set of criteria is a draft, and no further updates of it were found

α: Various products e.g. sprouts/fruits/vegetables

Disclaimer: The information provided in this table was retrieved from the documents available online and does not necessarily reflect the current official requirements of the stated countries. The data also include unpublished data supplied by other governmental departments, agencies and stakeholders

Note: Due to the term variations in non-English documents and the difficulty of finding the latest versions, it is recommended that the original references should be read to obtain a wide range of accurate information

Lebanon, Egypt, Morocco, Sudan, South Sudan, Palestine, Mexico, Iran and Pakistan. Furthermore, Nigeria and Argentina have published numerous online governmental articles on food regulation, but we found no set of microbiological criteria for food in these countries.

The interpretation of *E. coli* prevalence in food microbiological criteria is controversial. For example, the GSO 1016/2015 meat product criteria, section raw edible offal accepts when two out of five replicates of tested food (defined in the criteria) had concentrations equal to or less than 5×10^6 *E. coli* cfu/g (enumeration technique) under aerobic plate count, and rejects when *E. coli* O157 was found in meat product criteria, sections raw meat and raw minced [104]. The fact that *E. coli* O157 is not detected in *E. coli* numeration tests may lead to serious infection in consumers because it can cause serious infection in humans even within the accepted range mention above [143–145]. Probably the best practice is to test both *E. coli* enumeration and *E. coli* O157 detection, as mentioned by Turkey's, Singapore's and GSO 1016/2015 microbiological criteria (meat sections) indicated with both E/✓symbols in Table 2. For example, Brazil's and India's microbiological criteria do not require testing *E. coli* O157 in raw meat and require only *E. coli* enumeration [118–120, 125]. Brazil and India are among the biggest meat exporters to the Saudi Arabian market in 2017 [146]. According to the Saudi Food and Drug Authority (SFDA) database, in 2017, at least 6% of the tested meat products imported from Brazil and India were infected with *E. coli* O157:H7 (isolated from different manufacturers) [40]. This was probably because Brazil and India do not have microbiological criteria for testing *E. coli* O157 in raw meat before exporting.

Concluding remarks

E. coli is a potential source of benefits to humans, although it can also pose a threat. More than 80 potential reservoirs of *E. coli*, including pathogenic strains, are known due to its ability to adapt readily to many environments [147]. Accurate diagnostics of pathogenic *E. coli* can ensure that treatment is initiated during the early stages of infection. In this review, we propose a comprehensive structure of the classification of pathogenic and non-pathogenic *E. coli,* including the most important serotype O157. The result insights to provide a broad overview on sources of O157 and other pathogenic strains and the factors that may play a role in changing the classification (i.e. aEPEC, EHEC or STEC) of these strains. For instance, the O26 serotype derived from STEC causes HUS and HC, whereas, EPEC O26 causes less severe enteritis. This perhaps due to the fact that, EPEC O26:H11 does not possess the EAF plasmid that encodes BFP (classified as aEPEC) [15, 148]. Some STEC strains (termed EHEC), such as some of O157 isolates, have a LEE, which is involved in A/E lesions and intestinal colonization. However, other STEC strains, such as O113, are LEE negative (i.e. they do not possess an LEE) and are capable of causing vary infections in humans (Figure 2) [149]. STEC (LEE-negative) strains typically possess other adhesive factors, such as Saa, Iha, Efa1/LifA, Lpf and ToxB [149]. O113 as non-O157 and non-big six is also responsible for HUS (Fig. 2) [3, 149, 150]. EPEC genomes have recently been investigated. Depending on the acquisition of pEAF and LEE, EPEC is classified as EPEC1, EPEC2, EPEC3 or EPEC4, however, little is known about their specific classification and pathogenicity targets. In general, A/E lesions of EPEC are known to be involved in several animal-targeted serotypes, namely, rabbit entero-pathogenic *E. coli*, dog entero-pathogenic *E. coli* and porcine-enteropathogenic *E. coli* [7].

A distinguishing feature of EAEC is the production of EAST1 [3]. Some EAEC strains express the *stx2* gene, which is mainly produced by VTEC (STEC) [151]. Therefore, both EAEC and VTEC are suggested to be overlap. EAST1 is also produced by aEPEC [15], and its homologue, STa, is produced by ETEC [3]. Donnenberg (2002) and Sarker (2016) argued that EAEC does not overlap with ETEC and EPEC (Fig. 2). However, due to the fact that aEPEC, ETEC and EAEC produce EAST1, overlap among all these serotypes is suggested.

EIEC is a closely related serotype to *Shigella* spp [3]. Unlike VTEC, EIEC strains do not produce toxins. EIEC strains are considered invasive serotypes. The toxicity of EIEC strains is likely due to multiple effects of various plasmids. EIEC carries a 213 kb virulence-associated (*inv*) plasmid that is located in a sequence initially carried by four plasmids, highlighting its importance in virulence [3]. Moreover, some strains of EIEC possess *stx* and *eae* genes, which are produced mainly by VTEC (STEC) [15, 152], which points to overlap between EIEC and VTEC (Fig. 2).

The specific details in Table 1, specially regarding outbreak sources and severity offer valuable insights. Data reveals a rise in outbreaks linked contaminated water beside the well characterised source (undercooked food), it highlights the need for targeted interventions at that point in the contaminations' chain. Similarly, a rise in hospitalizations or HUS cases might indicate a potential shift in the severity of STEC infections.

These outbreaks emphasize the importance of strong public health measures, including promoting safe food handling practices, proper sanitation throughout the food chain and maintaining effective surveillance systems to detect and respond to outbreaks. By

prioritizing these measures, we can minimize the public health burden associated with STEC infections.

Recommendations

Countries should invest in PulseNet-like systems to enhance food safety, prevent outbreaks and protect public health. The microbiological criteria investigated in this review are currently applied in over fifty countries which equal almost one third of countries worldwide, therefore we recommend food-related authorities worldwide to generate and apply microbiological criteria on food matrix for better food quality.

Note (role of SFDA as a founder of this article)

Saudi Arabia is a major producer of chicken meat in GCC regions [79]. The food market in Saudi Arabia has been controlled by the Saudi Food and Drug Authority (SFDA) since 2003 in collaboration with other local authorities [146, 153]. Since the establishment of the SFDA, many new laws have been put in place to ensure the safety and quality of food. These include regulating the use of biological and chemical agents, requiring allergen labelling and establishing foodborne illness surveillance [154–156]. The SFDA has a large number of laboratories, which test food, drug and medical device products [157]. It has routine laboratories to evaluate the daily randomly inspected products, and reference laboratories, which target particular products over a long period of time to evaluate its safety (reference: SFDA official website).

Method of research

Literature data

Of the almost three thousand relevant online sources, nearly nine hundred fifty articles and books were revised and added to the Mendeley Library for referencing. Of these, one hundred and ten were used to gather information, which was added to this review.

Food microbiological criteria data

No criteria have been published with DOI numbers, which can lead to the loss of such files (references used in Table 2). Therefore, PDFs of freely available online criteria were added to the Zenodo online database and the DOI numbers 10448448 were generated to access the criteria, or thought the following link https://doi.org/10.5281/zenodo.10448448.

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Disclaimer
The views expressed in this paper are those of the author(s) and not do not necessarily reflect those of the SFDA or its stakeholders. Guaranteeing the accuracy and the validity of the data is a sole responsibility of the research team.

Author contributions
Dr. Meshari Ahmed Alhadlaq (M. A. A.) conceived and designed the study (from the Molecular Biology Section at the Reference laboratory for Microbiology Department 'RLM', Executive department of Reference laboratories, Laboratories and Research Sector, SFDA). M. A. A. and Othman I. Aljurayyad (O. I. A.) wrote the manuscript. M. A. A. rewrote the manuscript. All co-authors substantially edited and agreed for publication.

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