Six Serogroups of Non-O157 Shiga Toxin-Producing *E. coli*

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Non-O157 Shiga toxin-producing *Escherichia coli* (STEC) are emerging serogroups that often result in diseases ranging from diarrhea to severe hemorrhagic colitis in humans. The most common non-O157 STEC are O26, O45, O103, O111, O121, and O145. These serogroups are known by the name “big six” because they cause severe illness and death in humans and the United States Department of Agriculture declared these serogroups as food contaminants.

Escherichia coli non-O157 foodborne

1. *E. coli* Serogroup O26

Serogroup O26 *E. coli* possesses both EPEC and STEC strains. STEC O26 is the most common non-O157 serogroup related to HUS and HC in humans [1], while EPEC O26 is responsible for less-severe enteritis [2]. The human isolates of *E. coli* O26 mostly express the flagellar (H) antigen (e.g., H11) or are nonmotile (NM/H-) if the antigen is not encoded by their genome. Nevertheless, based on the molecular assessment, it has been proven that the H-serogroup is also classified under the H11 clonal complex [3]. EPEC O26:H11 does not comprise the EAF plasmid and is hence categorized as aEPEC [4]. However, classifying O26 serogroup into pathogroups, such as STEC and aEPEC, may be misleading, since aEPEC could be STEC which lacks *stx* and the reverse [5].

O26 serogroup has been isolated from both healthy as well as diarrheic animals [6][7][8]. Even though myriad studies on O26 have been performed, most of these investigations have been inadequate, with limited sample sizes, or have centered on STEC O26 rather than non-STEC O26 serotypes. Besides, most studies have been conducted on cattle [9][10], and research on O26 in sheep is scarce [7][11]. Among the STEC serogroups, O26 is the second most reported serogroup in several countries, including Ireland, Italy, France, and Denmark, and clinical O26 cases presently exceed cases caused by O157 [12]. Non-O157 infections were found to be clinically relevant in pediatric patients, in whom the disease severity is comparable to that of O157 [13][14]. Current outbreaks of *eae* and *stx2* positive O26:H11 serogroup have caused severe HUS infections in young individuals, particularly in some countries, including France, Italy, and Romania [15][16][17][18]. To date, in European countries, the O26:H11 serogroup is accountable for more HUS infections than O157 STEC serogroup and is of emerging importance [12].

2. *E. coli* Serogroup O45

STEC O45 serogroup is one of the top six non-O157 STEC that have been recognized as a cause of sporadic BD in humans [19]. During the first outbreak of STEC O45 in 2005, 52 inmates in New York City became ill with diarrhea or BD, probably because they had been exposed to an ill food worker [20]. In addition to these outbreaks, two other outbreaks caused by O45:H2 serogroup have occurred in which 18 illnesses were reported, and contaminated smoked goat and game meat was implicated as the source of contamination in both outbreaks [21]. In a different study, two O145:H28 strains (RM13716 and RM13714) caused ice cream and lettuce-associated outbreaks in Belgium and US, respectively. These strains shared a common ancestor with 5 different STEC O157:H7 strains, including the Japanese *E. coli* Sakai strain [22][23].

3. *E. coli* Serogroup O103

Among the other STEC serogroups of *E. coli*, O103 has caused a few outbreaks worldwide. STEC O103:H2 is one of the most prevalent STEC serotypes isolated from humans in Europe [24]. *E. coli* O103:H11 has been reported in Japan and Canada as a sporadic cause of human infections in addition to *E. coli* O103:H2 [25].

An *E. coli* outbreak caused by O103 occurred in Norway in the spring of 2006. Among the 17 cases identified, 10 children experienced HUS and one died. The outbreak was traced to a cured sheep sausage product from one brand [26]. S*tx*-producing *E. coli* O103 H2 was first isolated in Brazil from sheep in 2004 and re-emerged in 2005 [27]. During the period 1997–2000, STEC *E. coli* O103 H2/H (-) ranked third among the most repeatedly isolated EHEC types in Germany [28]. The pathogen has also been reported in sporadic outbreaks at nursery facilities in Japan between 2010 and 2013 [29]. Recent outbreaks of *E. coli* O103 have been reported in Germany following school-led trips to Austria [30]. In this case, raw cow's milk was implicated as the source of the infection, and international collaboration played an essential role in preventing outbreaks and responding appropriately.

4. *E. coli* Serogroup O111

Serogroup O111 causes enteropathogenic and enterohemorrhagic sickness in humans [31]. EPEC O111 serogroup is the leading cause of diarrhea in infants, predominantly in developing nations. Among the non-O157 *E. coli* serovars, *stx*-producing EHEC O111 is one of the frequent causes of BD and HUS across the world [32][33]. Many outbreaks have been correlated to this pathogen [19][32].

Research on the O111 serogroup that has originated from different sources indicated that there is a substantial phenotypic and genetic diversity among this *E. coli* O serogroup. Even though motile O111 serotypes isolated from children's diarrhea usually expressed flagella antigens (H2, H12, or H21), in several cases NM isolates have been encountered. Serogroup O111:H and O111:H2 characteristically carry the EAF plasmid that facilitates localized attachment (LA) of bacteria to cultured cells which is a feature of the classic EPEC serogroups.

The O111 clone was the first STEC serogroup of *E. coli* that cause gastroenteritis outbreaks in humans [34]. The flagellar type O111:H12, O111:H8, O111:H2, and the non-flagellated O111: NM has been recognized as pathogenic clones. The O111 antigen has been classically linked to the enteropathogenic serogroup and now has

also been recognized as an O antigen of EHEC and EAEC *E. coli* [31]. Due to the lack of facilities for proper diagnosis of O111 serotype of *E. coli*, the burden of the public health illness caused by these clones is underestimated. However, several O111 serotypes have been reported as they caused serious enteric illness in humans, including 28% of 50 outbreaks of child diarrhea in the US from 1934 to 1987 [35], 33% of infantile diarrhea cases in Brazil [36], a huge outbreak affecting >700 infected individuals in Finland [37], and currently, documented HUS outbreaks in Italy [38] and Australia [39].

5. *E. coli* Serogroup O121

S*tx*-producing O121 *E. coli* serogroups have been mainly isolated from individuals who developed HUS or HC, and consequently they are categorized as EHEC [40][41][42]. Moreover, these serogroups having virulence factors like those of enteroinvasive *Shigella* and *E. coli*, have resulted in shigellosis-like sicknesses [43]. In 1999, an HUS outbreak caused by O121:H19 serogroup was reported and the source of the infection was related to the lake in Connecticut [40]. Tarr et al. identified 24 isolates of O121:H19 serogroup and H- (NM) variants using multilocus sequencing and enzyme electrophoresis and the results indicated that the isolates were determined as a single bacterial clone. These isolates comprised a virulence gene that is specific for EHEC clones; nevertheless, the sequence analysis indicated that the O121:H19 clone was not classified under either EPEC *E. coli* or classical EHEC groups. Tarr et al. indicated that O121:H19 serogroup gained virulence genes and denotes a typical EHEC clone [44].

6. *E. coli* Serogroup O145

O145 is a crucial cause of HUS and HC worldwide. Ruminants are the main reservoir of this serogroup, which carry the agent in their hind GIT system and shed it in the manure. Fecal matter is the major source of carcass and hide contamination which leads to O145-associated foodborne infections in humans. Several outbreaks have been reported associated with O145 infection in the US and other countries, including Argentina [45], Germany [46], and Belgium [47]. In 1999, two O145-associated illnesses were reported in a daycare center in Minnesota, US [48]. This serogroup has also been reported as the cause of a waterborne infection in humans in 2005, in Oregon, US [49], and in 2010, the consumption of contaminated romaine lettuce resulted in a multistate outbreak, causing 45% hospitalization, associated with HUS in 10% of cases [50].

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