

Review article

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A BRIEF OVERVIEW OF EMERGENCIES AND DISSEMINATION OF SHIGA-TOXIN-PRODUCING *E. COLI* AND *SALMONELLA ENTERICA* SEROVAR TYPHIMURIUM DEFINITE PHAGE TYPE 104 IN HUMANS AND FOOD PRODUCING ANIMALS

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Abstract

Shiga-toxin-producing *Escherichia coli* (STEC) and *Salmonella enterica* serovar Typhimurium definite phage type 104 (DT104) are foodborne pathogens of public health significance. It is less known that Shiga-toxin-producing *Escherichia coli* (with cattle being the most probable natural reservoir) can be isolated from pigs, sheep and wildlife as well. The basic information about detection of Shiga-toxin-producing genes in STEC as well as the origin of *Salmonella* Typhimurium DT104 (STDT104), the virulence and resistance mechanisms including their distribution in the world are presented. Having in mind the foodborne transmission mechanisms we emphasize the role of veterinary scientists in Serbia in implementing good management practice on animal farms and in strengthening laboratory diagnostic capacities.

Key words: *E. coli*, shiga toxin, *Salmonella* Typhimurium, humans, food

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KRATAK PRIKAZ POJAVE I DISEMINACIJE *E. COLI* KOJA PRODUKUJE SHIGA TOKSIN I *SALMONELLAE* TYPHIMURIUM, FAGOTIP 104, KOD LJUDI I ŽIVOTINJA KOJE SE UZGAJAJU ZA ISHRANU LJUDI

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Kratak sadržaj

Šiga toksin produkujuće *Escherichia coli* (STEC) i *Salmonella enterica* serotip Typhimurium definitivni fagotip 104 (DT104) su hranom prenosivi patogeni od velikog značaja za javno zdravlje. Manje je poznato da se STEC sojevi, osim kod goveda (koji su procenjeni za njihove prirodne rezervoare), mogu naći i kod svinja, ovaca i divljači. U ovom radu sumiramo najznačajnije informacije o detekciji šiga toksina kod izolata STEC, poreklu *Salmonella* Typhimurium DT104 (STDT104), mehanizmima virulencije, rezistenciji na antibiotike i njihovoj rasprostranjenosti u svetu. Posebno ističemo potrebu većeg angažovanja veterinarske struke u implementaciji dobrog menadžmenta na farmama, kao i jačanju kapaciteta dijagnostičkih laboratorija u Srbiji.

Ključne reči: *E. coli*, šiga toksin, *Salmonella* Typhimurium, ljudi, hrana

INTRODUCTION

To this day, beyond 200 serological O:H types of Shiga-toxin-producing *E. coli* (STEC) have been identified. Among these isolates, serological types O26:H11, O103:H2, O111:H8, O145:H28, O91:H21 and O157:H7 were frequently isolated from patients with life-threatening conditions such as hemolytic uremic syndrome (HUS) and from patients suffering from bloody diarrhea (Beutin et al., 2004; Lim et al., 2010). However, new virulent serotypes for humans are continuously reported worldwide. The plasmid-mediated mechanism facilitates the adhesion of pathogenic *E. coli* to the proximal small intestine in infants (Wade et al., 1979). Intimin production is identified as the

major mechanism of virulence in *E. coli* O157:H7. Intimin leads to the attachment of bacteria to the host cell, and it is encoded by few genetic variants of the *eae* gene in pathogenic strains (Beutin et al., 2004). Other enhanced virulence traits participate in infection, transmission, colonizing capacity, acid resistance and environmental survival of the STEC as well (Law et al., 2000; Lim et al., 2010). Basic laboratory protocols for the detection of STEC include identification of genes encoding Shiga toxin represented by the *stx1* and *stx2* genes and detection of intimin-encoding gene *eae* or their variants and/or by simultaneous detection of enterohemorrhagic *E. coli* (EHEC) hemolysin gene *hly* (Arancia et al., 2019; Beutin et al., 2004).

It has been established that food producing animals may represent an important reservoir of STEC, but isolates highly pathogenic for humans (EHEC O157:H7) are not detected so frequently in domestic and wild animals. However, the carrier-status is often underestimated, which is due to the sensitivity of detection methods, and the shedding and transmission capacity of the EHEC O157:H7 in ruminants and non-ruminants. Nevertheless, EHEC O157 can contaminate and colonize vegetables and fresh fruits by evading plant defense mechanisms and also present possible reservoir of this infectious agent (Berger et al., 2010). Environmentally mediated transmission or direct contact from person to person represent possible route of infection in humans but to a much lesser extent (Ferens and Hovde, 2011). Cattle and birds get infected through contaminated environment, and birds can spread infection of pathogenic *E. coli* and *Salmonella* spp. to a long distance. The knowledge of the safe management systems is therefore required to minimize transmission of bacteria from species to species and from environment to humans, livestock and birds (Pedersen and Clark, 2007).

In this work, we emphasize the significance of STEC and we summarize recent knowledge about the most probable reservoirs of these pathogenic bacteria. We would like to point out the importance of regular monitoring of foodborne pathogens, especially STEC, in Serbia suggesting that serological typing, molecular genetics analysis of the strains and detection of virulence plasmid is needed to determine which one of them is particularly harmful for humans (Ferens and Hovde, 2011). In addition, the origin of STDT104 and their antimicrobial resistance features are briefly described.

INFECTION OF HUMANS WITH *E. COLI* O157:H7 AND NON O157

Shiga-toxin-producing *E. coli* also designated enterohaemorrhagic *E. coli* is an important pathogen because it causes invasive illness in humans. The

serotype O157:H7 was for the first time isolated from patients experiencing bloody diarrhea and abdominal pain. All patients consumed undercooked beef meat in sandwiches, and all *E. coli* isolates from patients and food were identified as a rare type *E. coli* O157:H7 (Riley et al., 1983). Today, this serotype is the most common cause of HUS in humans and sometimes, if infection is complicated, it can also cause death. As estimated by the Centers of Disease Control and Prevention (CDC) the O157:H7 serotype annually causes 60 deaths in the USA. Moreover, the annual cost of illness is estimated to 450 million dollars (Lim et al., 2010). However, other non-O157 serotypes such as O103, O26, O91 and O145 are identified in human gastroenteritis patients and food in Germany. The most common isolate from patients and food was O91, while the highest heterogeneity between human and food isolates was identified in O113 serotype. In humans, STEC O113:H4 was the most prevalent serotype, while STEC O113:H2 was the most frequent serotype isolated from food (Werber et al., 2008). However, in the study of Beutin et al., (2007), serological type's characteristics for human pathogenic *E. coli* including isolates carrying the *eae* gene was not commonly found in food samples in Germany.

Due to the detection models available, it is not always possible to properly identify *E. coli* causing human illness in non-O157 strains (Law et al., 2000). Hence, the exact number of human illnesses caused by *E. coli* infection may be underestimated. Genomic evolution in serotype O157:H7 includes the loss of genetic material, horizontal transfer of phage associated genes and ability to acquire the number of virulence genes (Lim et al., 2010). The population most susceptible to infection causing illness includes children less than 7 years of age, and the *eae* gene was most frequently found in their STEC or EHEC isolates. However, in older patients, the *eae* gene is not frequently detected. The reason is twofold as the protective immunity to intimin develops in humans that counter infection with STEC in early age and because of the occupational hazards due to the contact with STEC from animals, food and environmental sources (Beutin et al., 2004). Small number of STEC was detected in *E. coli* isolates from hospitalized and community patients in Dhaka city of Bangladesh possibly because protective immunity against STEC has developed. Out of 410 stool specimens from hospitalized patients only 2.2% isolates carried *stx* toxin genes. The *stx2* gene was found in four isolates, three isolates were *stx1* positive, and two isolates had *stx1* and *stx2* genes. All patients with STEC infection had uncomplicated diarrhea. Moreover, seven out of nine patients were diagnosed with *Vibrio cholera* infection. Similar findings were apparent in community patients - 11 out of 160 were *stx* gene positive, but mild diarrhea was the only clinical symptom. In total, five STEC of serotypes O32:H25,

O2:H45, O76:H19, ONT:H25 and ONT:H19 were identified. The *eae* gene was detected in only one isolate from hospitalized patient and in one isolate from community patient, while four isolates from both categories of patients had *hly*_{EHEC} gene (Islam et al., 2007).

ANIMAL RESERVOIRS OF SHIGA-TOXIN-PRODUCING *E. COLI*

Cattle are natural reservoir of the *E. coli* O157:H7 (Faith et al., 1996) but other domestic animals such as pigs, sheep, goats and turkeys are also shedding O157:H7 in feces (Lim et al., 2010). Interestingly, the *E. coli* O157:H7 was isolated from wildlife (Hofer et al., 2012; Singh et al., 2015) and game meat as well (Miko et al., 2009). Possible contact between wild and domestic animals or the contact of wildlife with the excrements from farms and farm environment may be the reason for interspecies transmission (Singh et al., 2015). STEC was found in imported meat in Malaysia (Abuelhassan et al., 2016) as well as in beef meat and contact surfaces in butchery shops in Sharkia province, Egypt (Darwish et al., 2018). All of these isolates carried *stx1* or *stx2* or both genes and belonged to various serotypes.

Since recently, attention has been given to the STEC isolates from pigs at slaughter in Italy. Most isolates possessed *stx2a*, *stx2b* and *stx2c* gene subtypes, while *stx2e* gene typical for pigs was detected in 25.8% of the isolates. It is also important to mention that none of the isolates possessed intimin-coding *eae* gene and it is not likely that the isolates belong to the serotypes often found in strains pathogenic for humans (Arancia et al., 2019). In another study from Italy, STEC O157 serogroup and non-O157 serotypes were not detected in any of the samples of the ready-to-eat food but were found in pig feces and not-ready-to-eat food (Bardasi et al., 2017). From the food samples of raw beef, lamb, pork and wildlife meat as well as raw milk and raw-milk cheese in Germany, none of the *E. coli* isolates were O157:H7 serotype; however, *stx2* and *stx2d* genes were commonly found in STEC isolate belonging to serology groups O22:H8, O91:H21, O113:H21, O174:H2, O174:H21, O178:H19 and O179:H8. Cattle are the most frequent reservoir of the STEC. Common serotypes O91:H21, O113:H21, O174:H2/H21 from food are also detected in human patients with HUS in Germany and other countries (Beutin et al., 2007). According to the study from Argentina 84% of STEC isolates of bovine origin belonged to the same serotype that is commonly found in humans. The *stx2* gene was most frequently found in STEC as it was detected in 74% of the isolates (Blanco et al., 2004). A comprehensive survey was undertaken in USA with the aim of detecting O157:H7 *E. coli* on major pig farms. Total

106 of the isolates from 2526 fecal samples were serotype O157 but only one isolate possessed *stx1* gene, and four isolates had *stx2* gene. Three isolates possessed the *eae* intimin gene. None of the isolates was identified as O157:H7 serotype (Feder et al., 2007). The antimicrobial resistance in *E. coli* O157 is not so pronounced as compared to commensal or other pathogenic strains such as avian pathogenic *E. coli* (APEC). In fact, among 361 *E. coli* O157 in the research work of Schroeder et al. (2002), the highest rate of resistance was established in isolates originating from pigs. The isolates were mostly resistant to trimethoprim-sulfamethoxazole, tetracycline and cephalothin. Similar antimicrobial resistance patterns were found in *E. coli* O157:H7 isolates from humans and cattle. The resistance among humans and cattle was most pronounced for sulfamethoxazole (9% versus 12%) and tetracycline (7% versus 11%). Resistance to ampicillin was established in 5% of human isolates and 1% of bovine isolates, while resistance to cephalothin was 4% versus 1%, and to chloramphenicol and amoxicillin-clavulanic acid it was 0% versus 1%.

Simultaneous detection of *Salmonella* spp. and STEC in retail raw ground beef in the USA is reported by using enrichment and commercial real-time PCR assay including colony confirmation. The problem in detecting STEC has occurred because, in some cases, the *stx* gene and *eae* gene were not carried by STEC identified as serology groups O26, O45, O103, O121, and O145. Also, other non-STEC *E. coli* strains may have *stx* and *eae* genes, but those isolates could not be assigned to STEC common serotypes by PCR. *Salmonella* spp. was detected by PCR in 28 samples (9.1%) and recovered in XLT-4 agar in 27 samples. Out of 10 serotypes obtained, only *S. Newport* was multidrug resistant. Hence, simultaneous detection of STEC and *Salmonella* spp. is possible by applying adequate enrichment medium and agar plates, and by applying real-time PCR (Wasilenko et al., 2014).

THE OCCURRENCE OF MULTIDRUG-RESISTANT *SALMONELLA* TYPHIMURIUM DT104

Salmonella Typhimurium definite phage type 104 isolates from food of animal origin, mostly beef meat, were first reported in United Kingdom (Wall et al., 1994). This phage type is multidrug resistant to ampicillin, chloramphenicol, streptomycin, sulfonamides and tetracycline (R-type ACSSuT) (Threlfall et al., 1996). Rapid worldwide spread of STDT104 has been documented over decades and STDT104 was assigned as a truly multidrug resistant epidemic clone (Threlfall, 2000). In 1998, Danish scientist reported the occurrence of STDT104 with reduced susceptibility to fluoroquinolones in human isolates

and those isolates were epidemiologically connected to the consumption of pork meat (Mølbak et al., 1999). At least two mechanism of resistance such as the efflux pump and multiple mutations on topoisomerase genes are implicated in resistance to fluoroquinolone antibiotics (Giraud et al., 2000). Antibiotic resistance gene cluster unique to STDT104 strain was detected in other phage types, such as DT120 and *Salmonella* serovar Agona (Cloeckaert and Schwarz, 2001). Horizontal transfer of resistance genes in serovar Typhimurium is worrisome and advocates the continuous monitoring all over the world. Recently, the whole genome sequencing approach has shed a new light to the epidemiology of STDT104. It was revealed that the common ancestor of the STDT104 emerged in 1948, and first reports of human infection dated from 1960. The global spread of STDT104 occurs from several reasons. The strain has zoonotic nature and is transmitted from species to species (involving terrestrial animals, humans, birds, aquatic animals). The genetic organization of *Salmonella* genomic island 1 (SGI1) is well studied and today we know that the 5' conserved segment consist of insertion sequence element IS6100 preceded by SGI1 and class 1 integron, the 5 bp direct repeats are surrounding multidrug resistance genes (MDR) and the GC content is higher in isolates carrying SGI1 with MDR comparing to SGI1 without MDR. Therefore, SGI1 is an intrinsic element in STDT104 while resistances genes were acquired later on depending of the distinctive geographic distribution of this strain which could lost or acquire additional resistance determinants (Leekitcharoenphon et al., 2016).

DIAGNOSTICS OF SHIGA-TOXIN-PRODUCING *E. COLI* AND *SALMONELLA* TYPHIMURIUM (DT104) IN ANIMAL ISOLATES IN SERBIA

STDT104 infection is still present worldwide in both human and animal population (Velhner et al., 2014). The occurrence in animals depend very much on disease eradication measures established in certain countries, with the aim to diminish STDT104 from poultry and livestock, as it was the case in Denmark (Leekitcharoenphon et al., 2016). Sporadic isolates of *S. Typhimurium* from poultry in Serbia are actually susceptible to antibiotics, which is quite surprising (Velhner et al., 2014). However, the number of isolates available for resistotyping and the lack of antimicrobial resistance monitoring system, which is now in the initial stage of development, probably do not provide the exact data on antimicrobial resistance in the serovar *S. Typhimurium* (DT104) in Serbia. The Institute of Meat Hygiene and Technology (IHTM) in Belgrade is the most reputable laboratory and the only one in the field of veterinary

medicine in Serbia certified for detection of Shiga-toxin-producing *E. coli* by applying ISO standard 13136:2012. Other laboratories should implement these methods and all suspect isolates should be sent to the IHTM for confirmation. STEC should be given particular attention also by Public Health Institutes in Serbia. Strengthening of laboratory capacity for diagnostic and establishment of referent laboratories is the prerequisite to avoid gaps in the diagnostics and research in Serbia.

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Author's contributions:

MV wrote the manuscript, BV, DT, MP, SVK, BP and DM read the manuscript and made corrections in the document.

Competing Interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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