

Pre-slaughter intervention by vaccination of cattle – new approach to reduce risk of meat contamination by foodborne pathogens, and consequently reduce incidence of human disease and economical burden*

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A b s t r a c t: Enterohaemorrhagic *Escherichia coli* (EHEC) is an important zoonotic pathogen of humans. It is a commonly found fecal coliform bacterium present in the intestine of ruminants, from where it is frequently shed into the environment. Cattle are the main reservoir of *E. coli* O157. Whilst causing no disease in cattle, exposure of humans to very few bacteria (10 or fewer) is responsible for major outbreaks of hemorrhagic colitis (HC) and haemolytic uremic syndrome (HUS) throughout the world. The most common mode of transmission of *E. coli* O157 to the human population is by consumption of contaminated food, which accounts for 61% of human illness. The United States Centres for Disease Control and Prevention (CDC; 2008) reported that consumption of beef products and produce (including fruits and vegetables) was a significant mode of transmission, accounting for 45% and 34% of food borne illnesses respectively. In addition to the foodborne mode of transmission, drinking contaminated water accounted for 15% of all cases of human illness associated with *E. coli* O157. In Canada approximately 26 000 people become ill each year because of exposure to *E. coli* O157.

Traditionally, work has focused on improving cattle meat safety through the implementation of post-harvest antimicrobial treatments. However for effective disease control in human populations, which are susceptible to *E. coli* O157 arising from not only contaminated beef, but contaminated produce, drinking water and direct contact, it becomes apparent that a comprehensive 'One Health' initiative is probably the most suitable approach to control or eliminate the amount of pathogens that enter our environment. This approach identifies and evaluates the connections between animals, human and environmental domains. The value of this approach is demonstrated by the data from CDC which estimates that three-quarters of all new and emerging diseases are zoonotic. Presently, *E. coli* O157, and several other enteric pathogens found in livestock including *Salmonella*, and *Campylobacter jejuni*, found in sheep, cattle swine and poultry, and *Yersinia enterocolitica* found in swine contribute to the estimated 79 million people in the United States that become ill after consuming food contaminated with pathogens.

An on-farm vaccination strategy is one of the best methods to reduce the prevalence of *E. coli* O157 both within in its primary host and the general environment. The focus of this manuscript is to describe *E. coli* O157, the central role of cattle in disseminating *E. coli* O157 in the environment, and the rationale for the development and implementation of an efficacious pre-harvest vaccination strategy using a fully licensed vaccine.

Key words: vaccination of cattle, meat contamination, foodborne pathogens.

Introduction

Enterohaemorrhagic *Escherichia coli* O157 (EHEC)

EHEC consists of a subset of *E. coli* strains that have acquired virulence factors and are pathogenic to humans. By definition *E. coli* O157 is used to

describe the subgroup of shiga toxin-producing *E. coli* that have the potential to cause haemorrhagic colitis (HC) in humans.

In cattle, the terminal rectal mucosa in the colon, located at the recto-anal junction (RAJ), has been identified as the principal site of *E. coli* O157 colonization (Naylor *et al.*, 2003). The RAJ con-

*Plenary paper on International 56th Meat Industry Conference held from June 12-15th 2011. on Tara mountain;

*Plenarno predavanje na Međunarodnom 56. savetovanju industrije mesa, održanom od 12-15. juna 2011. godine na Tari.

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tains the highest concentration of this organism and contributes more to the fecal load of bacteria than the rest of the gut combined. Other sites of *E. coli* O157 colonization include the rumen, small intestine, and the proximal colon. An important aspect of colonization is the formation of attaching and effacing lesions (A/E lesions) which involves host cell cytoskeletal rearrangements, and pedestal formation at the sites of bacterial attachment. Central to these mechanisms is the Type III secretion system, described in the next section.

The critical virulence factor for *E. coli* O157 is their ability to produce shiga toxins (Stx). These toxins are synonymously called vero toxins (VT) due to their specific cytotoxicity to Vero cells (African green monkey kidney cells). Consequently the *E. coli* bacteria that produce VT are called verotoxin producing *E. coli* (VTEC) or Shiga toxin-producing *E. coli* (STEC). These designations, VT/Stx and VTEC/STEC, are used interchangeably.

Major virulence factors

Shiga toxins (stx)

Shiga toxins are synthesised by gram negative bacteria, including *E. coli* O157. In the human, cell surface Stx glycolipid receptors, Gb3 (globotriaosylceramide) and Gb4 (globotetraosylceramide) are present on glomerular endothelial and other vascular endothelial and epithelial cells and play a major role in the pathogenesis of human disease including hemorrhagic colitis (HC) and hemolytic uremic syndrome (HUS). Based on toxin-neutralization and nucleotide sequence analyses shiga toxins are classified in two major groups, Stx1 and Stx2, showing approximately 60% nucleotide sequence identity. Generally, Stx2 has been more closely associated with severe disease and HUS, and has been shown to be 1000 times more toxic to human renal endothelial cells, than VT1 (Moxley, 2004 for review).

In mature cattle, after *E. coli* O157 challenge the degree of colonization is dependent on age of cattle, challenge duration and magnitude, however the mechanisms behind these different colonization rates are not fully understood. Research by Lowe *et al.*, 2009, determined that *E. coli* O157 strain origin, from either human or bovine, lineage type and stx2 expression all affect the amount of *E. coli* O157 colonization in the intestines of cattle. Stx2 promotes the intestinal colonization of *E. coli* O157 in cattle through an increased expression of non Tir colonization sites and toxicity to the absorptive epithelial cells. In cattle although stx2 increases colonization, it is not cytotoxic to the cells of the

jejuna and descending colon of cattle (Bains *et al.*, 2008).

Type III Secretion System

The type III secretory system (TTSS) is the mechanism for translocation of bacterial proteins into host cells. The TTSS enable *E. coli* O157 to adhere to enterocytes causing histopathological lesions, called ‘attaching and effacing lesions’ (A/E lesions) which are characterized by localized destruction of the brush border microvilli, enabling *E. coli* O157 to attach intimately to the plasma membrane of host epithelial cells. Once attached the bacteria stimulate host cell actin polymerization and rearrangement of the cytoskeletal architecture, forming an attachment pedestal which secures it to the host cell.

The genes that encode the A/E lesions are located in a region of the genome called the ‘locus of enterocyte effacement’ (LEE). The LEE of *E. coli* O157:H7 is 43 kb and an additional region of 7.5kb prophage sequence, not found in other EHEC. The arrangement of the 41 genes is in three distinct regions. The first region encodes TTSS, the second region encodes an adhesion molecule and its translocated receptor, and finally the third region encodes several translocated molecules.

The bacterial TTSS is an essential component of the host-pathogen interaction, a major feature of TTSS is the translocation of a variety of virulence factors from within the bacterium into the host cell via a filamentous needle complex spanning the bacterial and host cell membranes, whereby the bacteria are able to inject their proteins, called effectors into the host cell. Once injected, the proteins can modify the function of the host cell.

The proteins that comprise the TTSS apparatus comprise the structural proteins. Other proteins called ‘translocators’ serve the function of translocating another set of proteins into the host cell, for example an adhesion molecule called intimin and its translocated receptor, called Tir, which is a bacterial outer membrane protein encoded by *eaeA*. Collectively, translocated proteins are called ‘effectors’ since they are the virulence factors that effect the changes in the host cells, allowing the invading pathogens to colonize and multiply in the host.

A subset of TTSS are the translocated secretory proteins, *E. coli* secretory proteins (Esp). These effector proteins including, Map, EspF, EspG, EspH, EspB and sepZ, modify the host cell signal transduction mechanisms during the formation of A/E lesions. When translocated into the host cell, they elicit a variety of reactions resulting in diarrhoea and

transmigration of acute inflammatory cells to the infection site (Coburn *et al.*, 2007).

Of particular interest is the secretory protein, EspA. Its function is to form the filamentous, hollow needle-like structure that assembles as a physical bridge between bacteria and host cell surfaces, which functions as a physical conduit for the translocation of bacterial effectors into host cells. After translocation of effector proteins, the filamentous complex is removed from the bacterial cell surface. This is necessary to make room for the intimate bacterial attachment between intimin and Tir that is essential for the A/E lesions (Lim *et al.*, 2010).

E. coli O157 has been regarded as causing no clinical or subclinical signs of infection in cattle. However, recent evidence indicates that *E. coli* O157 is not strictly a commensal bacterium in the bovine host. Experimental infection with high doses of *E. coli* O157:H7 causes diarrhoea, with A/E lesions in neonatal calves and transient watery diarrhoea in weaned calves. Histopathological damages, A/E lesion formation and enterocyte remodeling associated with removal of the epithelial layer at the site of colonization have been recorded in cattle that are persistent shedders (Nart *et al.*, 2008). Generally the relative resistance of cattle to the systemic effects of Stx may be explained by the observation of Hoey *et al.*, 2003, who found that unlike in the human, Stx Gb3 receptors only present in the proliferating crypt cells of bovine intestines, and not in the vascular cells.

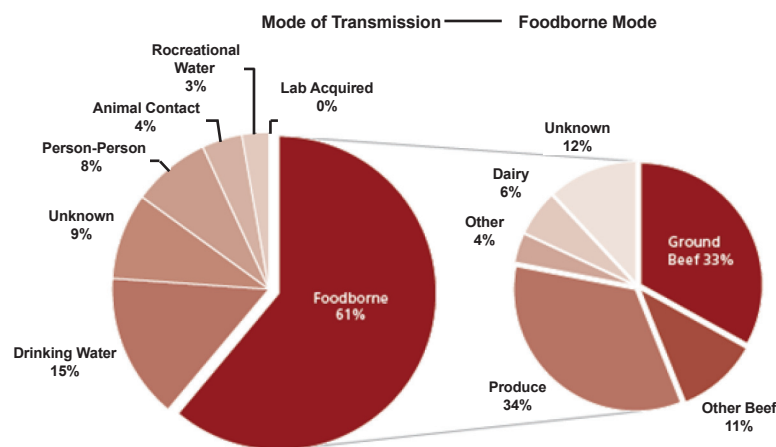
Source of Human Infection

{TC “Source of Human Infection” \f C \l “2”}

Recent data and outbreaks have shown that *E. coli* O157 is capable of contaminating a variety of foods, and this knowledge has increased our understanding that multiple interventions are needed to reduce the risk of infection (LeJeune 2007; Khanna, 2008). According to the CDC (2008), 61% of human illnesses from *E. coli* O157 are foodborne and 15% are caused by consuming contaminated drinking water. Ground beef (33%) and produce (34%) are the two most frequent causes of foodborne illnesses (Figure 1).

Direct human/animal contact accounts for a significant number of *E. coli* O157 infections. A survey of thirty-two U.S. agricultural fairs demonstrated that *E. coli* O157 is widespread in animals at these exhibits (LeJeune, 2004): *E. coli* O157 was isolated from livestock at 97% of the fairs tested, with 11% of cattle testing positive.

The distribution of VTEC cases in Ontario, Canada, were studied to evaluate geographic relationships between livestock density and human VTEC incidence. Study results show a seasonal pattern of illnesses with higher rates from April to October than in winter (July is the peak). The data also showed a positive relationship between the incidence rate of VTEC illness in a community and cattle density. Data from Scotland found a similar relationship between bovine shedding of *E. coli* O157 and human illnesses (Pearce, 2009; Ferens and Hovde, 2011).



Source: Centers for Disease Control and Prevention (CDC, 2008)

Figure 1. Sources of *E. coli* O157 Illness
Slika 1. Izvori oboljenja *E. coli* O157

Prevalence and estimated cost of human illness in Canada

{TC “Human Illness – Primary Outcomes” \f C \l “2”}

HC is characterized by abdominal cramping and watery diarrhea, which may turn into bloody diarrhea and fever. On average, 2% to 7% of these cases progress, becoming HUS, however, numbers have reached as high as 15% (*Center for Foodborne Illness Research and Prevention*, 2009). A portion of patients with HUS develop End Stage Renal Disease (ESRD) and die.

In Canada, VTEC infections confirmed through laboratory analysis must be reported to the Public Health Agency of Canada (PHAC). The rate of confirmed infections in Canada was 3.36 per 100,000 population. Using the model developed by *Frenzen* (2005) and the PHAC data, we estimate that each year Canada has 26,209 cases of *E. coli* O157 infection. Estimates for the actual annual number of illnesses resulting from *E. coli* O157, indicate that between 10 and 47 cases exist within the community for every positive case reported (*Thomas*, 2006). Based on the number of infections annually and Canadian health care cost information, the total cost of VTEC illness in Canada is estimated to be \$29.6M (*Foodborne Illness cost calculator, United States Department of Agriculture*, 2006; Table 1).

Table 1. Cost of VTEC-related Illness to Canada
Tabela 1. Troškovi VTEC- u odnosu na bolest u Kanadi

Medical Costs/ Medicinski troškovi	Lost Productivity and Premature Death/ Gubitak produktivnosti i preвременa smrt	Total/ Ukupno
\$3,627,956	\$26,014,184	\$29,687,139

On-Farm Prevalence

{TC “On-Farm Prevalence” \f C \l “2”}

A review of existing studies demonstrates prevalence rates of animals testing positive for *E. coli* O157 ranging from 9% to 88% (*Karmali* 2010). This wide range exists both within and between herds. A study conducted on Ontario beef cow-calf farms found *E. coli* O157 at 52% of farms surveyed (*Cernicchiaro* 2009). Based on that study, the author concluded in an interview with Canadian Cattlemen magazine (2010) that “farmers need to assume that

the organism [i.e., *E. coli* O157] is present on their farm”.

The concentration at which *E. coli* O157 is shed in feces varies from animal to animal and ranges from 10^2 to 10^5 cfu/g. Within a herd of cattle is a sub group referred to as ‘super shedders’, shedding $>10^4$ cfu/g. These animals contribute disproportionately to the *E. coli* O157 burden in a herd. Models of transmission dynamics have demonstrated that more than 80% of *E. coli* O157 spread arises from less than 20% of the most infectious individual cattle.

Presence of a ‘super-shedder’ on a farm has been associated with a high proportion of low-level shedding by other herd members. *Matthews* (2006) report that cattle exposed to a super-shedder increase shedding of *E. coli* O157 six fold in other cattle housed in the same pen. DNA evidence shows that these super-shedders transmit *E. coli* O157 to animals housed in the same pen. Super-shedder cattle represent the greatest risks of contaminating the food chain and maintaining high prevalence of *E. coli* O157 within cattle populations.

Rational for pre-harvest intervention

Interventions currently employed to minimize or eliminate the risk of human illness from *E. coli* O157 are focused on the harvest and processing segments within the beef industry (*Rogan et al.*, 2008). Hides are the key source of carcass microbial contamination (*Keen et al.*, 2002), and lairage at the processing plant are a major source of hide contamination, rates of hide contamination increase from 50.3% to 94.4% between the time cattle were loaded onto tractor-trailers at the feedlot and the time hides were removed in the processing plant. *E. coli* O157 prevalence on hides is associated with prevalence on pre-evisceration carcasses (*Elder et al.*, 2000).

Effective vaccination would presumably have its greatest impact on super-shedders, which, although low in proportion, are the most important transmission vector. Blocking colonization on super-shedders not only reduces shedding and hide contamination in those animals, but simultaneously reduces risk of contaminating co-penned animals. Likewise, a vaccination strategy aimed at reducing super-shedder numbers can simultaneously reduce the risk of carcass contamination associated with presence of super-shedders in truckloads of animals being transported to slaughter.

Together these data suggest a role for on-farm control of *E. coli* O157 to reduce the pathogen load entering the plant, our environment and ultimately to reduce human exposure to the pathogen.

The United States Department of Agriculture's Food Safety Inspection Service modeling paper demonstrated that vaccinating cattle was a cost effective intervention strategy for reducing EHEC associated illness in humans (Withee *et al.*, 2009) using vaccine efficacies ranging from 50% to 100%. Although data generated through this risk assessment and economic analysis showed a different break-even point at each efficacy level, there was a consistent reduction in human illness.

*Econiche*TM Vaccine Efficacy

Bioniche, in collaboration with Dr. Brett Finlay, University of British Columbia, and the Vaccine and Infectious Disease Organization developed and fully licensed a vaccine (*Econiche*TM) for use in healthy cattle. The vaccine has been shown to reduce the shedding of *E. coli* O157 in cattle. The vaccine targets the type III secretory system (TTSS), which is essential for *E. coli* O157 attachment in the recto anal junction of cattle.

The studies of Potter, 2004, Rogan, 2007, Rogan 2009, and Allen, 2011 have shown this approach to be efficacious in reducing the amount of shedding of *E. coli* O157. Controlled challenge studies demonstrate that vaccinating cattle with *Econiche*TM results in:

1. reduction in number of days the bacterium is shed in the feces
2. 64% reduction in duration of shedding
3. 71% reduction in the proportion of animals shedding
4. 2.28 \log_{10} reduction in number of bacteria shed in the feces.

Although calves usually do not have high titers to TTSS proteins, vaccination with *Econiche* does result in the production of serum antibodies against EspA, Tir and total Type III secretory proteins after vaccination at day 0, 21 and 42, see Figure 2. Overall the challenge studies clearly demonstrate that that vaccination of cattle is an effective approach to reduce pre-harvest *E. coli* O157 burden in cattle. The value of this approach is to reduce the quantity of *E. coli* in the environment and reduce hide and carcass contamination, allowing the benefits of HACCP to be fully realized.

The efficacy of *Econiche*TM has been evaluated under field conditions where cattle are naturally exposed to *E. coli* O157 during summer months. A 2004 feedlot study demonstrates that animals vaccinated under field conditions are 98% less likely to be colonized by *E. coli* O157 in the terminal rectum mucosa, resulting in a vaccine efficacy of 92.3% (Peterson, 2007).

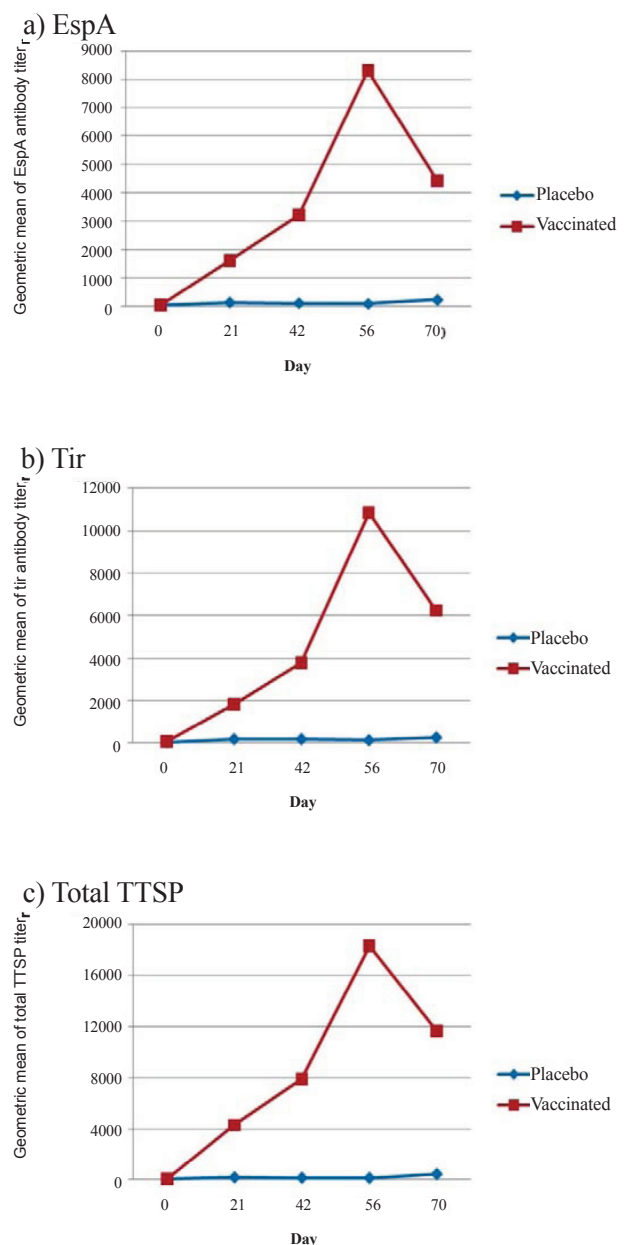


Figure 2. Serum titres of antibodies against EspA, Tir, and total type III secreted protein (TTSP) for 30 placebo-treated calves and 30 calves vaccinated with 3 doses of a TSP vaccine, calculated from the geometric mean with the use of $\log_{10}(\text{titre} + 1)$ values.

Slika 2. U serumu antitela protiv titre EspA, TIR, a ukupan tip III luči protein (TTSP) za 30 lečenih placebo teladi i 30 teladi vakcinisanih sa 3 doze vakcine TSP, računajući od geometrijska sredina uz korišćenje LOG10 (Titre + 1) vrednosti

A large-scale study across nineteen commercial feedlots was also conducted in 2004 to evaluate efficacy of 2 vaccinations, one upon entry to the feedlot and a second at re-implantation of hormones. This study demonstrates that, compared to unvaccinated

cattle on a per pen basis, vaccinated cattle have a 92% lower probability of being colonized by *E. coli* O157 and are less likely to test positive, indicating that the vaccine reduces environmental exposure of cattle to *E. coli* O157 (Smith, 2008).

While it is clear that reducing *E. coli* O157 in the feedlot and environment is best achieved by reducing shedding of the organism in the feces, there is a strong correlation between hide removal and subsequent prevalence on the carcass. In order to evaluate the effect of vaccination on hide contamination, a feedlot study was conducted in 2005. The hides of cattle vaccinated with Econiche™ were found to be 58% less contaminated than control animals (Smith, 2009).

A large-scale clinical vaccine trial (Smith, 2009) of commercially fed cattle in 2005 tested the efficacy of vaccinating all cattle in a feed yard using a two-dose regimen of Econiche™. Five hundred and four cattle were randomly assigned to 63 pens within three treatment regions in the feed yard. The researchers concluded that the two-dose regimen effectively reduces *E. coli* O157 fecal shedding and hide contamination. This same study also demonstrates that vaccinating at least some cattle within each feed

yard region provides greater protection against hide contamination than commingling vaccinates and non-vaccinates.

Conclusion

While vaccination has beneficial short-term effects at the packing plant, in reducing carcass contamination, it has a longer term effect at the feedlot or farm level. By dramatically reducing colonization at the terminal rectal mucosa, vaccination also reduces the probability for environmental transmission of *E. coli* O157 within commercial farm operations (Smith et al., 2008), thus gradually limiting the re-infection cycle within the herd.

The reduction of on-farm *E. coli* O157 through vaccination could also reduce the risk of contaminating produce or wells via run-off of water contaminated by manure or slurry, thereby limiting the potential of transmitting the pathogen to people. On-farm vaccination against *E. coli* O157 is an important component of the comprehensive 'One Health' initiative designed to keep our environment healthy for all to prosper in.

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Vakcinacija goveda pre klanja kao preventivna mera – novi pristup smanjenju rizika od kontaminacije mesa patogenima koji se prenose hranom, i smanjenje pojave bolesti kod ljudi i ekonomske štete

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Rezime: Enterohemoragična *Escherichia coli* (EHEC) je važan zoonotska bakterija kod ljudi. To je fekalna koliformna bakterija koja je obično prisutna u crevima preživara, odakle dospeva u spoljašnju sredinu. Goveda su glavni rezervoar *E. coli* O157. Dok kod goveda ne izaziva nikakva oboljenja, izlaganje ljudi veoma malom broju bakterija (10 ili manje) izaziva pojavu hemoragičnog kolitisa (HC) i hemolitičkog uremičnog sindroma (HUS) širom sveta. Najčešći način prenošenja *E. coli* O157 na ljudsku populaciju je konzumiranjem hrane, što čini 61% oboljevanja kod ljudi. Centar za kontrolu i prevenciju bolesti SAD (CDC; 2008) izveštava o tome da je konzum od govedeg mesa kao i drugih prehrambenih proizvoda (uključujući voće i povrće) predstavljalo značajan način prenošenja bolesti, i to 45% i 34% od svih bolesti koje se prenose hranom, respektivno. Pored prenošenja bolesti hranom, konzumiranje kontaminirane vode je činilo 15% svih slučajeva oboljevanja ljudi od *E. coli* O157. U Kanadi, približno 26.000 ljudi oboljeva svake godine zbog dolaska u dodir sa *E. coli* O157.

Tradicionalno, aktivnosti su usmerene ka poboljšanju bezbednosti mesa goveda kroz implementaciju antibakterijskog tretmana pre klanja. Međutim, za efikasnu kontrolu bolesti u ljudskoj populaciji koja je podložna oboljevanju od *E. coli* O157 i to ne samo od kontaminiranog govedeg mesa, već i kontaminiranih prehrambenih proizvoda, postaje očigledno da sveobuhvatna inicijativa “Jedno zdravlje” je verovatno najpogodniji pristup kontroli i uklanjanju patogena koji dospevaju u našu sredinu. Ovaj pristup identifikuje i ocenjuje veze između domena životinja, ljudi i životne sredine. Vrednost ovog pristupa demonstriraju podaci CDC koji ocenjuju da tri četvrtine svih nobih bolesti koje se pojavljuju su zoonoze. Trenutno, *E. coli* O157, kao i nekoliko entero bakterija koje se mogu naći u domaćim životinjama, uključujući *Salmonella*, i *Campylobacter*

jejuni, koje se mogu naći u ovcama, govedima, svinjama i živini, kao i *Yersinia enterocolitica* koja se nalazi kod svinja, doprinose oboljevanju 79 miliona ljudi u SAD nakon konzumiranja hrane koja je kontaminirana patogenima.

Strategija vakcinacije na farmi je jedna od najboljih metoda za smanjenje preovladavanja *E. coli* O157 u njenom primarnom domaćinu, kao i u životnoj sredini. Fokus ovog rada je bio opis *E. coli* O157, centralne uloge goveda u širenju *E. coli* O157 u prirodi, i razlog za razvoj i implementaciju strategije efikasne vakcinacije pre klanja, korišćenjem potpuno licencirane vakcine.

Ključne reči: vakcinacija goveda, kontaminacija mesa, patogeni prenosivi hranom.

Paper recieved: 9.05.2011.