

Where the Hell did Shiga Toxin *E. coli* come from? A Literature Review – Part 1

In recent months, a surge of papers have appeared in the literature describing findings from the deadly 2011 *E. coli* O104:H4 outbreak in Germany linked to sprouts (2-10, 12-14). The speed at which this information is being published in the literature—much of it free to the public through open access journals—is a testament to the advances in biotechnology available to scientists that study emerging foodborne pathogens. However, despite all the impressive molecular tools the researchers' have at their disposal, the origin of the unusual strain associated with the outbreak in Germany is still unknown. In fact, the origin of *E. coli* O157:H7, a bacterium first described in the 1970s and currently the most well studied shiga toxin-producing *E. coli* (STEC) strain, also (despite conventional wisdom) remains elusive.

Introduction

So, I ask, where the hell did *E. coli* O157 and other STECs come from?

If you read the media stories and foodist blogs, it would seem that this question has been answered with total certainty. The popular belief is that “superbugs” in the food system are the product of industrial agriculture. The dogma is that feedlots (also called concentrated animal feeding operations or CAFOs), grain-feeding, and genetically modified organisms (GMOs) are the root cause of everything wrong in our food system including food safety problems.

For example, Michael Pollen said in a 2010 editorial, “The Food Movement Rising” (11):

“The 1993 deaths of four (sic, three) children in Washington State who had eaten hamburgers from Jack in the Box were traced to meat contaminated with E. coli O157:H7, a mutant strain of the common intestinal bacteria first identified in feedlot cattle in 1982.”

But, Dr. Thomas Whittam (1954-2008), a pioneer in the study of *E. coli* O157:H7 evolution, said in a 1998 paper published in *Emerging Infectious Diseases* (15):

“It has been proposed that an increased mutation rate (indicated by the frequency of hypermutable isolates) has facilitated the emergence of Escherichia coli O157:H7. Analysis of the divergence of 12 genes shows no evidence that the pathogen has undergone an unusually high rate of mutation and molecular evolution.”

Then in 2011, Dr. Eric Denamur, a French expert in the ecology and evolution of microorganisms, pointed out in *Clinical Microbiology and Infection* that the shiga toxin-producing *E. coli* German outbreak teaches us a lesson in genome plasticity (5):

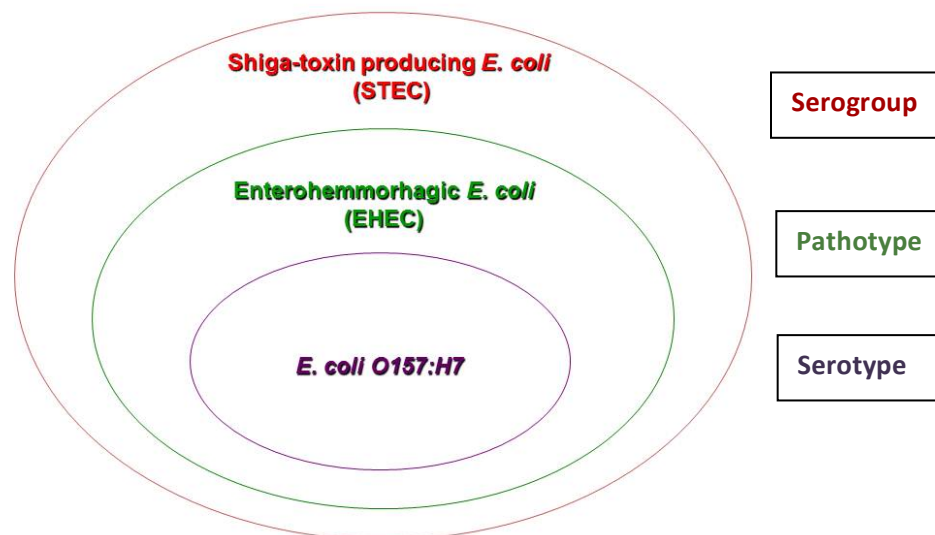
“The main lesson from this outbreak is that we should be aware of the capacity of the E. coli species to produce new combinations of genes, leading to the emergence of highly aggressive strains. Furthermore, antibiotic pressure in human and veterinary medicine should be kept as low as possible, as it will select for such strains once they become resistant.”

So, I jumped into the literature to gain a deeper understanding of the question about the origin of *E. coli* O157:H7 and other STECs, especially the role industrial agriculture may or may not have played in their evolution and emergence as human pathogens. What was the ultimate answer to the question of whether STECs are old or new pathogens, and where they arose? I would have loved a clear answer, but only came up with “it depends.”

This 3-part series summarizes my findings from the literature review.

Terminology

[*Escherichia coli*](#) was named after its discoverer, Theodor Escherich. The current terminology and nomenclature (naming) of *E. coli* strains can be confusing. There are over 700 *E. coli*



“serotypes” described. Most of these *E. coli* strains are harmless inhabitants of the intestinal tract of humans and other warm-blooded animals (1).

An *E. coli* serotype is named based on its numbered “O” (letter capital “O,” not zero) and “H” antigen types. *E. coli* O157:H7 is the prototype of a subset of pathogenic strains called enterohemorrhagic *E. coli* (EHEC). EHEC is a “pathotype” associated with human infections that may cause gastrointestinal and hemorrhagic symptoms such as bloody diarrhea and hemolytic uremic syndrome (HUS). *E. coli* O157:H7 and other EHEC pathotypes belong to a broader group of *E. coli* called shiga toxin-producing *E. coli* (STEC) as shown in the figure. Members of the STEC “serogroup” carry shiga toxin genes (*stx1* and/or *stx2*). STEC strains (including *E. coli* O157) are found primarily in healthy animal hosts (e.g., cattle, goats, sheep, pigs, deer, elk). The harmful strains may be transmitted to humans through contaminated food, water, contact with infected animals, or person-to-person transmission via fecal-oral ingestion.

Interestingly, according to recent research in Germany (2), the *E. coli* O104:H4 strain linked to raw sprouts is a combination of two different pathotypes: entero-aggregative *E. coli* (EAEC) and EHEC. A proposed name for the new pathotype is entero-aggregative-hemorrhagic *Escherichia coli* (EAHEC). It is unknown if the natural reservoir of this new EAHEC type is of human or animal origin.

Bacterial Evolution

Understanding the terminology used in describing *E. coli* strain relationships is important in deciphering the research into STEC evolution, including how fast these strains mutate into new variants. Serotyping is based on differences in surface antigens, which are likely encoded by genes that evolve slowly. In contrast, “virulence factors” describe generally a broad group of molecules or proteins that affect the bacteria’s ability to cause disease in humans. Shiga toxins and proteins or enzymes that confer antibiotic resistance are examples of virulence factors. Virulence factors are usually encoded by genes in the bacteria’s chromosomal DNA, or genes encoded by bacteriophage or plasmid DNA carried inside the bacteria. The ability of some of these virulence factor genes to move rapidly between different populations of *E. coli* may explain short-term changes in the virulence potential of some strains.

In Part 2, the discovery of *E. coli* O157:H7 and evidence of long and short-term evolutionary changes influencing its emergence as a human pathogen will be explored. In Part 3, evidence for and against the importance of agriculture practices (e.g., feedlots, GMOs) in the spread of *E. coli* O157:H7 and other STECs will be reviewed.

References

1. Boyce TG, Swerdlow DL, and Griffin PM. (1995). *Escherichia coli* O157:H7 and the hemolytic-uremic syndrome. N. Engl. J. Med. 333:364-368.
2. Brzuszkiewicz, E., A. Thurmer, J. Schuldes, A. Leimbach, H. Liesegang, F. D. Meyer, J. Boelter, H. Petersen, G. Gottschalk, and R. Daniel. 2011. Genome sequence analyses of two isolates from the recent *Escherichia coli* outbreak in Germany reveal the emergence of a new pathotype: Entero-Aggregative-Haemorrhagic *Escherichia coli* (EAHEC). Arch Microbiol 193:883-91.
3. Chattaway, M. A., T. Dallman, I. N. Okeke, and J. Wain. 2011. Enteroaggregative *E. coli* O104 from an outbreak of HUS in Germany 2011, could it happen again? J Infect Dev Ctries 5:425-36.
4. Cheung, M. K., L. Li, W. Nong, and H. S. Kwan. 2011. 2011 German *Escherichia coli* O104:H4 outbreak: whole-genome phylogeny without alignment. BMC Res Notes 4:533.
5. Denamur, E. 2011. The 2011 Shiga toxin-producing *Escherichia coli* O104:H4 German outbreak: a lesson in genomic plasticity. Clin Microbiol Infect 17:1124-5.
6. Feng, P., S. D. Weagant, and S. R. Monday. 2001. Genetic analysis for virulence factors in *Escherichia coli* O104:H21 that was implicated in an outbreak of hemorrhagic colitis. J Clin Microbiol 39:24-8.
7. Frank, C., D. Werber, J. P. Cramer, M. Askar, M. Faber, M. an der Heiden, H. Bernard, A. Fruth, R. Prager, A. Spode, M. Wadl, A. Zoufaly, S. Jordan, M. J. Kemper, P. Follin, L. Muller, L. A. King, B., Rosner, U. Buchholz, K. Stark, and G. Krause. 2011. Epidemic

- profile of Shiga-toxin-producing *Escherichia coli* O104:H4 outbreak in Germany. N Engl J Med 365:1771-80.
8. Jackson, S. A., M. L. Kotewicz, I. R. Patel, D. W. Lacher, J. Gangiredla, and C. A. Elkins. 2011. Rapid Genomic-Scale Analysis of *Escherichia coli* O104:H4 Using High-Resolution Alternative Methods to Next Generation Sequencing. Appl Environ Microbiol.
 9. Kemper, M. J. 2012. Outbreak of hemolytic uremic syndrome caused by *E. coli* O104:H4 in Germany: a pediatric perspective. Pediatr Nephrol 27:161-4.
 10. Mellmann, A., D. Harmsen, C. A. Cummings, E. B. Zentz, S. R. Leopold, A. Rico, K. Prior, R. Szczepanowski, Y. Ji, W. Zhang, S. F. McLaughlin, J. K. Henkhaus, B. Leopold, M. Bielaszewska, R. Prager, P. M. Brzoska, R. L. Moore, S. Guenther, J. M. Rothberg, and H. Karch. 2011. Prospective genomic characterization of the German enterohemorrhagic *Escherichia coli* O104:H4 outbreak by rapid next generation sequencing technology. PLoS One 6:e22751.
 11. Pollan M. The Food Movement Rising, The New York Review of Books, June 10, 2010, Available at: <http://www.nybooks.com/articles/archives/2010/jun/10/food-movement-rising/?page=1>
 12. Qin, J., Y. Cui, X. Zhao, H. Rohde, T. Liang, M. Wolters, D. Li, C. Belmar Campos, M. Christner, Y. Song, and R. Yang. 2011. Identification of the Shiga toxin-producing *Escherichia coli* O104:H4 strain responsible for a food poisoning outbreak in Germany by PCR. J Clin Microbiol 49:3439-40.
 13. Rasko, D. A., D. R. Webster, J. W. Sahl, A. Bashir, N. Boisen, F. Scheutz, E. E. Paxinos, R. Sebra, C. S. Chin, D. Iliopoulos, A. Klammer, P. Peluso, L. Lee, A. O. Kislyuk, J. Bullard, A. Kasarskis, S. Wang, J. Eid, D. Rank, J. C. Redman, S. R. Steyert, J. Frimodt-Moller, C. Struve, A. M. Petersen, K. A. Krogfelt, J. P. Nataro, E. E. Schadt, and M. K. Waldor. 2011. Origins of the *E. coli* strain causing an outbreak of hemolytic-uremic syndrome in Germany. N Engl J Med 365:709-17.
 14. Rohde, H., J. Qin, Y. Cui, D. Li, N. J. Loman, M. Hentschke, W. Chen, F. Pu, Y. Peng, J. Li, F. Xi, S. Li, Y. Li, Z. Zhang, X. Yang, M. Zhao, P. Wang, Y. Guan, Z. Cen, X. Zhao, M. Christner, R. Kobbe, S. Loos, J. Oh, L. Yang, A. Danchin, G. F. Gao, Y. Song, H. Yang, J. Wang, J. Xu, M. J. Pallen, M. Aepfelbacher, and R. Yang. 2011. Open-source genomic analysis of Shiga-toxin-producing *E. coli* O104:H4. N Engl J Med 365:718-24.
 15. Whittam T.S., S.D. Reid, and R.K. Selander. 1998. Mutators and long-term molecular evolution of pathogenic *Escherichia coli* O157:H7. Emerg Infect Dis, 4:615-7.