EDITORIAL

Deconstructing a Lethal Foodborne Epidemic

Martin J. Blaser, M.D.

Beginning in early May 2011, northern Germany was the principal site of a massive epidemic of bloody diarrhea and the hemolytic–uremic syndrome caused by Shiga-toxin–producing *Escherichia coli*. By the time the outbreak ended in early July, there were reports of more than 4000 illnesses, 800 cases of the hemolytic–uremic syndrome, and 50 deaths in Germany and in 15 other countries. As a result of remarkable efforts by public health officials, clinicians, and microbiologists who raced to control the outbreak and to treat its victims, much was learned. As reported in this issue of the *Journal* by Frank et al.[1] and Buchholz et al.,[2] as well as by other investigators elsewhere,[3-5] here is what we now know.

The outbreak was associated with a single clone of a strain of enterohemorrhagic *E. coli* classified as O104:H4. Although similar strains had been reported to cause the hemolytic–uremic syndrome before,[6] the 2011 strain was novel, with an uncommon serotype, plasmid-encoded extended-spectrum beta-lactamase (ESBL), and genes from enteroaggregative *E. coli*. Although Shiga toxin primarily causes tissue injury, the strain may have been aided by genes from enteroaggregative *E. coli* that improved its efficiency in intestinal colonization, and the presence of ESBL enhanced survival when beta-lactam antibiotics (including penicillins and cephalosporins) suppressed competitors. The epidemic strain apparently arose from precursors by sequential introduction of pathogenetic elements.[4] Whereas variants often arise in nature, only some can spread. This O104:H4 strain was well armed for mayhem and reminds us that evolution is a constant.

The outbreak was foodborne in contaminated sprouts. The initial investigation pointed to other uncooked salad foods, illustrating the difficulty in identifying vehicles in multisite outbreaks when exposures occurred days earlier and when answers are needed immediately.[7] The chain of transmission appears to have begun in Egypt, with fecal contamination of fenugreek seeds by either humans or farm animals during storage or transportation, perhaps as long ago as 2009. The seeds then went to a European distributor and from there to farms in several countries. During sprout germination, bacteria multiplied and moved from farm to restaurants and consumers, as Buchholz et al. extensively detail in their study. The evidence for such a series of events is compelling, even though the organism was not identified at the earliest steps, since the trail often is cold in point-source outbreaks by the time investigators are able to conduct trace-back investigations.[8] The modern commerce in food allows multiple opportunities for bacterial replication, and mass production and wide nets of distribution foster large, geographically diverse outbreaks.[9]

The outbreak began suddenly in early May, peaked within weeks, and ended in early July,[1] a pattern most consistent with a single point source. With the primary transmission being foodborne and the secondary transmission through household, nosocomial, and even laboratory vectors, cases continued to occur. Unlike most outbreaks of enterohemorrhagic *E. coli* that cluster in young children and the elderly, most cases occurred in adults across a broad age span. Although such a transmission pattern may mostly reflect the

implicated vehicle and food choices, the age distribution also suggests a lack of previous immunity to a novel pathotype. The long median incubation period (8 days) in contrast to other outbreaks of enterohemorrhagic *E. coli* (3 to 4 days)[10] may indicate either that relatively small inocula were consumed or that in vivo characteristics of the outbreak strains were atypical. The latter is most likely on the basis of the strain genotype, as well as incubation, age, and virulence characteristics. The predominance of the outbreak in women may only reflect food preferences, since the secondary cases were more evenly divided according to sex.

The outbreak was unusual, with an atypical age distribution, a long incubation period, very high rates of the hemolytic–uremic syndrome and death, and somewhat different clinical features in children and adults. The hemolytic–uremic syndrome developed suddenly, about 5 days after the onset of diarrhea. Such a window provides an opportunity to intervene in order to minimize illness, if only we knew what to do.

In this outbreak, clinicians cared for their patients diligently but without critical knowledge. Would antibiotics help or hurt? Glucocorticoids? Plasma exchange? Just as there is a system for emergency case reporting in Germany and elsewhere, we also need authorizations to conduct clinical trials in real time during public health emergencies such as this one. Patients should be randomly assigned to various clinically suitable regimens to learn what works and what does not. Infectious disease epidemics constantly arise, usually involving familiar pathogens but with combinations of known and unknown virulence factors or in new vehicles, causing novel outbreaks and clinical consequences. With our complex global food trade and multiple opportunities for microbial amplification, the next large outbreak is just around the corner. We can prepare for it by drafting generic nationwide (or worldwide) protocols with preapproval by institutional review boards (e.g., for outbreaks of enterohemorrhagic *E. coli*) so that we can learn while trying to mitigate these tragedies.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

From the Departments of Medicine and Microbiology, New York University Langone Medical Center, and the New York Harbor Department of Veterans Affairs Medical Center — all in New York.

This article (10.1056/NEJMe1110896) was published on October 26, 2011, at NEJM.org.

1. Frank C, Werber D, Cramer JP, et al. Epidemic profile of Shiga-toxin–producing *Escherichia coli* O104:H4 outbreak in Germany. N Engl J Med 2011. DOI: 10.1056/NEJMoa1106483.
2. Buchholz U, Bernard H, Werber D, et al. German outbreak of *Escherichia coli* O104:H4 associated with sprouts. N Engl J Med 2011. DOI: 10.1056/NEJMoa1106482.
3. Bielaszewska M, Mellmann A, Zhang W, et al. Characterisation of the Escherichia coli strain associated with an outbreak of haemolytic uraemic syndrome in Germany. Lancet Infect Dis 2011;11:671-6.
4. Mellmann A, Harmsen D, Cummings CA, et al. Prospective genomic characterization of the German enterohemorrhagic Escherichia coli O104:H4 outbreak by rapid next generation sequencing technology. PLoS ONE 2011;6(7):e22751.
5. Aldabe B, Delmas Y, Gault G, et al. Household transmission of haemolytic uraemic syndrome associated with Escherichia coli O104:H4, south-western France, June 2011. Euro Surveill 2011;16:19934.
6. Morabito S, Karch H, Mariani-Kurkdijian P, et al. Enteroaggregative, Shiga toxin-producing Escherichia coli O111:H2 associated with an outbreak of hemolytic-uremic syndrome. J Clin Microbiol 1998;36:840-2.
7. Barton Behravesh C, Mody RK, Jungk J. 2008 outbreak of Salmonella Saintpaul infections associated with raw produce. N Engl J Med 2011;364:918-27.
8. Herwaldt BL, Beach MJ. The return of cyclospora in 1997: another outbreak of cyclosporiasis in North America associated with imported raspberries. Ann Intern Med 1999;130:210-20.
9. Blaser MJ. How safe is our food? Lessons from an outbreak of salmonellosis. N Engl J Med 1996;334:1324-5.
10. Slutsker L, Ries AA, Greene KD, Wells JG, Hutwagner L, Griffin PM. Escherichia coli O157:H7 diarrhea in the United States: clinical and epidemiologic features. Ann Intern Med 1997;126:505-13.