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The 2011 Shiga toxin-producing *Escherichia coli* O104:H4 German outbreak: a lesson in genomic plasticity

E. Denamur[1,2]

1) INSERM, UMR-S 722 and 2) Sorbonne Paris Cité, UMR-S 722, Faculté de Médecine, Univ. Paris Diderot, Site Xavier Bichat, Paris, France

E-mail: erick.denamur@inserm.fr

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Escherichia coli is known as a versatile bacterial species encompassing both commensal and intraintestinal and extraintestinal pathogenic strains. An *E. coli* genome contains between 4200 and 5500 genes, with <2000 genes being conserved among all strains of the species (the core genome). Also, the pan-genome (i.e. all of the non-orthologous genes found in the species) consists of almost 20 000 genes [1]. Continuous gene flux has occurred during *E. coli* divergence, as a result of horizontal gene transfers and deletions confined to a small number of conserved positions in the chromosome. This chromosomal plasticity accelerates the adaptation of *E. coli* to varied environments and lifestyles, as it allows multiple gene combinations that, with epistatic interactions, result in phenotypic diversification.

The outbreak of bloody diarrhoea and haemolytic–uraemic syndrome in Germany in May and June 2011, caused by an *E. coli* O104:H4 strain [2], dramatically illustrates this tremendous *E. coli* genome plasticity. Owing to the advances in high-throughput sequencing technologies, several complete sequences of isolates from the outbreak were determined within a few days in China and in Germany [3]. It appears that the strain, which belongs to the B1 phylogenetic group of *E. coli* [4], is of multilocus sequence type (ST)678 (http://mlst.ucc.ie) and exhibits an O104:H4 serotype [5]. It shares 93% of its sequence with another O104:H4 ST678 strain, *E. coli* 55989, that was isolated in the 1990s in Bangui (Central African Republic) from a human immunodeficiency virus-infected adult with chronic diarrhoea [1,6]. Surprisingly, this 55989 strain is an enteroaggregative *E. coli* (EAEC) strain, with genes encoding proteins involved in the biogenesis of aggregative adherence fimbriae, which mediate the adherence of EAEC to the intestinal mucosa [7]. The German outbreak strain, which can be considered as an enterohaemorrhagic *E. coli* (EHEC) strain according to the disease that it causes, has acquired, since its divergence from the 55989 strain, the phage-mediated Stx2 Shiga toxin but not the locus of enterocyte effacement located on a 35-kb pathogenic island usually present in EHEC, allowing the attaching bacteria to efface the microvilli. It also possesses, like the 55989 strain, several characteristics of extraintestinal pathogenic *E. coli* (ExPEC) (https://www.genoscope.cns.fr/agc/microscope/home/index.php) [8]. It has the high-pathogenicity island, involved in iron capture, that has been shown to spread within the species by horizontal gene transfer, implicating homologous recombination [9], and the adhesin-coding gene *iha* in close vicinity to the siderophore-encoding gene *aer*, both of which present in the virulent emerging clone O25b ST131 [10]. In this regard, the 55989 strain is virulent in a mouse model of septicaemia, as it killed ten mice of ten inoculated [1]. In addition, the German outbreak strain has acquired resistance to numerous antibiotics, including third-generation cephalosporins, owing to several plasmid-borne genes, such as the extended spectrum β-lactamase CTX-M gene [2], which has been spreading dramatically in *E. coli* across the world in the last 10 years [11]. Fortunately, antibiotics are not indicated for treatment of the human disease, as they release the toxin, worsening the symptoms. In sum, it appears that the outbreak strain is an illustration of the genomic plasticity of *E coli*, with the acquisition of genes providing from different *E coli* pathovars (EAEC, EHEC, and ExPEC) and the acquisition of antibiotic resistance.

But what is the origin of this strain? Stx2-positive EAEC strains were previously described in Bangui during the same study that allowed isolation of the 55989 strain, although other characteristics of these strains, such as the serotype and ST, were not provided [6]. Sporadic cases of Stx2 O104:H4 ST678 strains causing diarrhoea and haemolytic–uraemic syndrome were reported in 2001 in Germany [12], in 2004 in France, in 2005 in South Korea [13], in 2009 in Georgia, and in 2010 in Finland [5]. Unlike classic EHEC, which has cattle as its reservoir, EAEC seems to have humans as its reservoir. An organic sprout farm near Hamburg has been incriminated [14] in the actual outbreak, but the exact mechanism of contamination needs to be determined.

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.

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Transparency Declaration

The author declares that he has no conflict of interest.

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