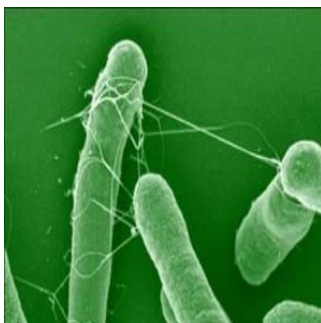


German E. Coli Code Cracked: Rapid, High-Tech Study of Ongoing Epidemic Creates New Paradigm for Outbreak



A team led by University of Maryland School of Medicine Institute for Genome Sciences researchers has unraveled the genomic code of the E. coli bacterium that caused the ongoing deadly outbreak in Germany that began in May 2011.

To date, 53 people have died in the outbreak that has sickened thousand in Germany, Sweden and the U.S. The paper, published July 27 in the New England Journal of Medicine (NEJM), describes how researchers around the globe worked together to use cutting edge technology to sequence and analyze the genomics of E. coli samples from the outbreak as well as closely related strains in a matter of days. They combined those findings with their knowledge of the biology and evolution of the bacteria to learn more about the outbreak. The analysis occurred rapidly enough to inform the physicians treating people who were infected, and assisted epidemiologists as they raced to trace the source of the pathogen. The research may be the first time that such a comprehensive scientific analysis of an emerging pathogen took place in the first days and weeks of an outbreak, according to the study's lead author, David A. Rasko, Ph.D., assistant professor of microbiology and immunology at the University of Maryland School of Medicine, and a research scientist at the Institute for Genome Sciences.

"This technology is evolving extremely rapidly, enabling us to accomplish much more accurate analysis with unprecedented speed," says Dr. Rasko. "It took years and millions of dollars to sequence the first E. coli genome more than a decade ago. Here we are, just months from the start of the German E. coli outbreak, and we've published a paper on it. This paper and the research it describes represent the new paradigm of outbreak investigations." The researchers collaborated with Pacific Biosciences of California, Inc., a Menlo Park-based company that used its new Single Molecule Real Time technology to sequence the genome of the E. coli strain from the German outbreak. The collaboration also included scientists from the Statens Serum Institute, the World Health Organization Collaborating Centre for Reference and Research on Escherichia coli and Klebsiella in Denmark, as well as Harvard and the University of Virginia.

"The University of Maryland School of Medicine has a global presence spanning 23 countries, and we are proud that our Institute for Genome Sciences has played a leading role in investigating this international health crisis and improving human health worldwide," says E. Albert Reece, M.D., Ph.D., M.B.A., vice president for medical affairs of the University of Maryland and the John Z. and Akiko K. Bowers Distinguished Professor and dean of the School of Medicine. Dr. Rasko and colleagues at the Institute for Genome Sciences analyzed the genomic data using computational tools, some of which were developed at the Institute. The Institute for Genome Sciences team included postdoctoral researchers Jason Sahl, Ph.D., and Susan Steyert, Ph.D., and lab manager Julia Redmond. Dr. Rasko's expertise is in the molecular pathogenesis and evolution of E. coli, which helped his team to interpret the massive amount of genomic data involved and learn more about the microbe and how it fits into the overall picture of E. coli.

Scientists found that the genome of the German outbreak E. coli strain was mostly enteroaggregative E. coli, a subtype of the bacteria. In carefully examining its genome, they found that the outbreak strain was actually an unusual combination of enteroaggregative E. coli and another subtype, known as enterohemorrhagic E. coli. Researchers also noted that the strain carried a unique set of virulence and antibiotic resistant factors, making it distinct from other strains of the bacteria. "This is not just a genome paper. It also examines the virulence and biology of the microbe," says Dr. Rasko. "Early in the outbreak, scientists described bacteria as a 'hybrid' strain. This strain is not a true hybrid, because it contains only a small amount of DNA sequence from enterohemorrhagic E. coli. We have not seen these kinds of unique combinations very often in the past. I expect we are going to see them increasingly, now that technology like Pacific Biosciences' has advanced to the point that we can sequence more strains very rapidly and relatively inexpensively."

"The combination of speed, accuracy and cost will lead genomic sequencing to be a diagnostic tool quicker than anyone currently envisages," says Dr. Sahl, the paper's co-author. When the outbreak began in May, scientists around the world began examining the E. coli strain as soon as samples were available. Many groups were releasing their findings to the public for free -- the data in the current study are also publicly available -- which resulted in a type of "crowd-sourcing." That is, research was being conducted through the collaboration of a large, disparate group around the globe. "Usually, science takes place in relative isolation," says Dr. Rasko. "This is the first time we've seen true 'open source' analysis of a microbial genome."

Very early on in the outbreak, German scientists used another sequencing technology and preliminary analysis to determine was unique about the pathogen associated with the outbreak. In fact, they identified a gene that produced a toxin associated with the very symptoms doctors saw in patients, such as severe diarrhea. This gene, known as the Shiga toxin, is produced more when certain antibiotics are used. The findings meant that patients' symptoms would worsen when they were treated with antibiotics. Those initial findings immediately began to inform clinical care, as doctors stopped using antibiotics to treat infected patients. "Our research is a more detailed, comprehensive analysis than that early research," says Dr. Rasko. "This was an international collaboration pulled together in a matter of days. I expect we will see more collaborations like this to deal with new emerging pathogens in the future." The NEJM paper will provide new, detailed information to assist researchers and physicians as they continue to investigate the ongoing E. coli outbreak in Europe.

"It's exciting to be at the forefront of genomics like this," says Dr. Rasko. "This research was a chance for us to leverage the power of the Institute for Genome Sciences to help create a new paradigm for the study of microbes and outbreaks. It also has implications for genomics as a tool in routine diagnostics.

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Journal Reference:

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PHOTO: *E. coli*. (Credit: James P. Nataro, M.D., Ph.D., M.B.A.)

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