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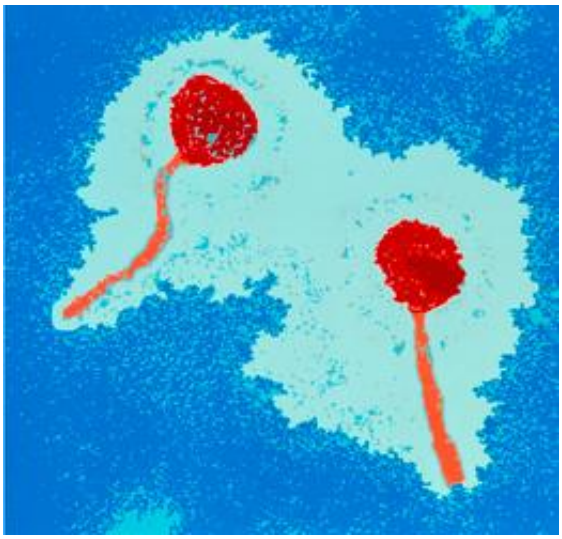
News

Phage on the rampage

Antibiotic use may have driven the development of Europe's deadly *E. coli*.

Marian Turner

Women, beansprouts, cucumbers, bacteria, cows: the cast of the current European *Escherichia coli* outbreak is already a crowd. Enter the phage. Bacteriophages are viruses that infect bacteria, and they are star players in the chain of events that led to this outbreak.



Escherichia coli bacteria become dangerous to humans when they are infected by Shiga-toxin-producing bacteriophages.

DR GOPAL MURTI/SCIENCE PHOTO LIBRARY

Bacterial infections often originate from contaminated food, but it is now about six weeks since the start of this outbreak and the trail is going cold. It's hard to be sure of the culprit — but this simply serves to highlight the importance of understanding how infectious bacteria get into the food chain in the first place.

Case-control studies of patients in the German outbreak pointed to salad vegetables, and both cucumbers and beansprouts have been suspects. It is possible that the vegetables were contaminated with bacteria originally carried in soil or water; but the more likely source of the bacteria is animals. Pathogenic *E. coli* are typically passed to humans from ruminant animals (cows or sheep) via faecal contamination in the food chain or through consumption of raw milk or meat products.

But how do pathogenic *E. coli* arise in the first place? This is where bacteriophage come in. The bacterium in this outbreak, currently recognised as strain O104:H4, makes Shiga toxin, which is responsible for the severe diarrhoea and kidney damage in patients whose *E. coli* infections develop into haemolytic uremic syndrome (HUS). The genes for the Shiga toxin are not actually bacterial genes, but phage genes being expressed by infected bacteria. So when an *E. coli* bacterium gets infected with a Shiga-toxin-producing phage, it becomes pathogenic to humans.

Our use of antibiotics may be helping those viral genes to spread. If bacteria are exposed to some types of antibiotics they undergo what is called the SOS response, which induces the phage to start replicating. Active replication of the phage causes the bacterial cells to burst open, which releases

the phage. It also releases the toxin, which is why antibiotics are not usually used to treat *E. coli* infections (see '**Europe's E. coli outbreak: time for the antibiotics?**').

The cost of protection

One of the many unusual characteristics of strain O104:H4 is that it has resistance genes to multiple classes of antibiotics. This suggests that wherever the bacteria have come from, there has been selective pressure to resist antibiotics. Heather Allison, a microbiologist at the University of Liverpool, UK, and David Acheson, a managing director for food safety at consulting firm Leavitt Partners in Washington DC, agree it is plausible that exposure to antibiotics — in agricultural use or in the environment — might be enhancing the spread of Shiga-toxin-producing phage.

"We are seeing more and more Shiga-toxin-producing strains."

Acheson worked on this question when he led a research group at Tufts University in Medford, Massachusetts, studying the molecular pathogenesis of Shiga-toxin-producing *E. coli* in the 1990s. He says they saw Shiga-toxin-producing phage transfer between *E. coli* in response to sub-therapeutic levels of the antibiotic ciprofloxacin in vitro and in the intestines of mice.

"They do it in the laboratory," he says, "but it's hard to show it happens in the environment." He is convinced it does, though. "The potential for the creation of new pathogens via phage release is absolutely a factor in the broader environmental danger of overuse of antibiotics."

Agricultural use of antibiotics is a possible suspect. "Phage are particularly abundant in the guts of ruminants", says Alfredo Caprioli, from the European Reference Laboratory for verotoxin-producing *E. coli* in Rome, Italy (verotoxin is another name for Shiga toxin). And the gut is one place in which the phage move between different bacteria, and new pathogenic bacterial strains emerge.

Shiga toxins have been causing diarrhoeal disease in humans for centuries — the bacterial genus *Shigella* and the Shiga toxins were first named for Kiyoshi Shiga, a Japanese medical doctor who identified the bacterium during an outbreak of dysentery in Japan in 1897. According to Allison, Shiga-toxin producing phage probably picked up the genes encoding Shiga toxin from these bacteria, and since the 1980s have been spreading these virulent genes to other bacteria, including many strains of *E. coli*.

"We are seeing more and more Shiga-toxin-producing strains," says Alison Weiss, microbiologist at the University of Cincinnati in Ohio.

How have Shiga-toxin-producing phage spread so widely in just a few decades? Allison says they have

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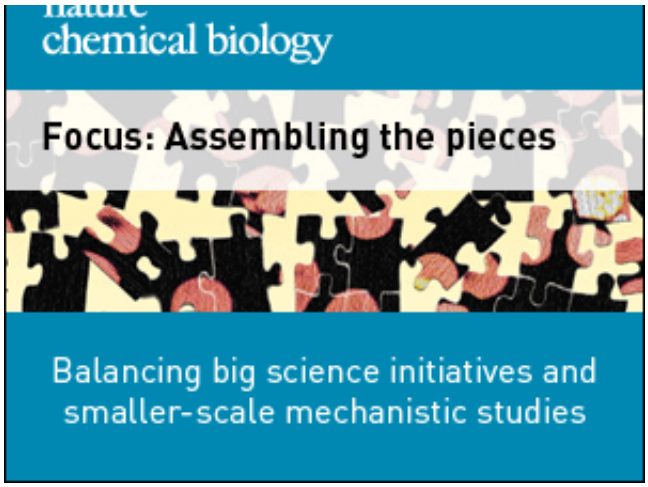
unusual characteristics that make them very successful. They infect bacteria by binding to a protein called BamA on the surface of many bacterial cells, which gives them a broad range of hosts. Most phage can only infect a host cell once, but Shiga-toxin-producing phage can infect the same cell multiple times, giving them greater pathogenic potential. And they can survive outside their hosts, in water or soil, for example.



Weiss adds that carrying the phage also provides a survival advantage for the host bacteria. "Once the bacteria are out in the environment — say in manure — they are fed on by other microbes, such as protozoans. The toxins kill the other microbes, giving these bacteria an advantage."

Not only are more *E. coli* strains being infected with Shiga toxin, but it seems to be moving into different classes of bacteria. The genome of strain O104:H4 has been sequenced, and it shares many genes with enteroaggerative *E. coli* (EAEC) strains. "EAEC strains are not typically associated with zoonotic infections, and EAEC and Shiga toxin is a very unusual combination," says Caprioli.

This increased movement of Shiga-toxin-producing phage means that even more unusual and dangerous strains could be on the horizon.

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I love the title of this news article. **#23795**
Paige Brown, Twitter@FromTheLabBench

Report this comment Posted by: **Paige Brown** | 2011-06-10 12:47:18 AM

"Women, beansprouts, cucumbers, bacteria, cows: the cast of the current European Escherichia coli outbreak is already a crowd. Enter the phage." **#23873**

Reminds me of Greg Bear's superb book on phage "Darwin's Radio" [another superb title, like this article] that also had a (highly) disproportionate end impact on women! It may have been sci-fi but it read like a very

plausible future... Highly recommended reading.

Anyway, back to today's reality: this article highlights (though not confirms) what I suspected about a possible link between agricultural use of antibiotics and new strains of resistant bacteria. Expect much more of this to come in future as the cost of food rises due to demand from fast growing countries!

Report this comment Posted by: **tas yoto** | 2011-06-11 05:19:58 PM

Several scientific sources suggested that the antibiotic resistance spectrum of this E. coli strain is so broad that this type of antibiotic resistance cannot develop naturally but is the result of directed mutagenesis. Sequences from Yersinia pestis were also alleged to be present in this strain. Members of the European Parlament are calling for an investigation into potential bioterrorism. Governments should lunch an investigation into these claims of potentially intentional release of a weaponized microorganism into the food chain. **#24014**

Report this comment Posted by: **peter grandics** | 2011-06-14 02:13:46 PM

"Escherichia coli bacteria become dangerous to humans when they are infected by Shiga-toxin-producing bacteriophages." **#24015**

I hope you mean that the phages carry the gene for the toxin. We biologists tend to sloppiness in our use of language.

Report this comment Posted by: **Wales P. Nematollahi** | 2011-06-14 02:14:48 PM

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