in gonorrhoea. In the United States, around 25% of gonorrhoea cases are caused by tetracycline-resistant bacteria. Elsewhere, rates of resistance are higher, with studies reporting rates closer to 60% or 70% in Europe[1,2].

Molina expects that the effectiveness of doxyPEP against gonorrhoea will depend on the rates of resistance in the local community and will probably decline over time as resistance levels rise.

But Luetkemeyer says that early results from a second French trial, called DOXYVAC, show doxycycline reduces gonorrhoea infections — in spite of high resistance levels. The results suggest that the drug still prevents an infection from taking hold, even if it is ineffective at treating an established infection. "It often takes a lot less of a drug to prevent a disease than it does to cure a disease," she says.

Doxycycline resistance has not emerged in chlamydia or syphilis. Working out whether doxyPEP leads to resistance in these infections could take years, says Molina.

"It often takes a lot less of a drug to prevent a disease than it does to cure a disease."

Luetkemeyer and her colleagues have collected swab and stool samples to see if people using doxycycline as a preventive tool alters the community of microorganisms that live in the gut or increases antibiotic resistance. Those results will be presented at a conference in February 2023.

One hope is that doxyPEP use in MSM could lower rates of bacterial STIs in the broader community — including in women, who bear the greatest effects of chlamydia and gonorrhoea infections — just as HIV-PrEP has done for HIV in high-income countries.

But Kenyon is sceptical that doxyPEP will lower STI rates, which can remain stubbornly high even after large-scale interventions.

Since Molina and his colleagues published results of the first doxyPEP study in 2018, people have been using doxycycline off-label as a preventive tool, he says. Kenyon fears that doxyPEP could expose people to the antibiotic for years or even decades.

For people already using doxyPEP, public-health recommendations are unlikely to convince them to stop, says Kohli. After Luetkemeyer's presentation at the International AIDS Conference in July, the US Centers for Disease Control and Prevention published information to guide the use of doxyPEP. The agency says it will publish subsequent guidance when the final data are published and reviewed.

1. Molina, J.-M. *et al. Lancet Infect. Dis.* **18**, 308–317 (2018).
2. Merrick, R. *et al. Euro Surveill.* **27**, 2200057 (2022).

CRISPR TOOLS FROM VIRUSES COULD BOOST GENE EDITING

Thousands of phages have DNA-cutting systems, probably picked up from microbial hosts.

By Heidi Ledford

A systematic sweep of viral genomes has revealed a trove of potential CRISPR-based genome-editing tools.

CRISPR–Cas systems are common in the microbial world of bacteria and archaea, where they often help cells to fend off viruses. But an analysis published on 23 November in *Cell* finds CRISPR–Cas systems in 0.4% of publicly available genome sequences from viruses that can infect these microbes (B. Al-Shayeb *et al. Cell* **185**, 4574–4586; 2022). Researchers think that the viruses use CRISPR–Cas to compete with one another — and potentially to manipulate gene activity in their host to their advantage.

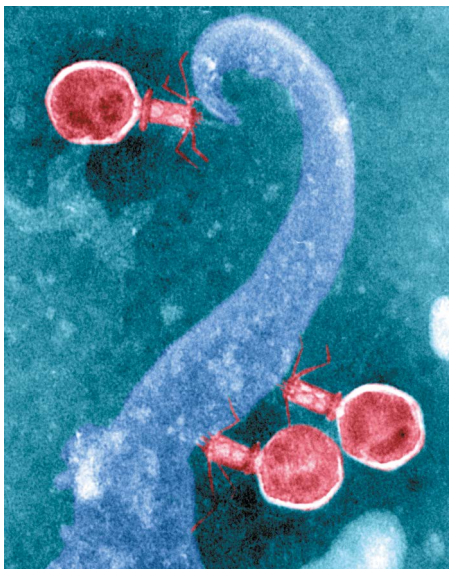
Some of these viral systems were capable of editing plant and mammalian genomes, and possess features — such as a compact structure and efficient editing — that could make them useful in the laboratory.

"This is a significant step forward in the discovery of the enormous diversity of CRISPR–Cas systems," says computational biologist Kira Makarova at the US National Center for Biotechnology Information in Bethesda, Maryland. "There is a lot of novelty discovered here."

DNA-cutting defences

Although best known as a tool used to alter genomes in the laboratory, CRISPR–Cas can function in nature as a rudimentary immune system. About 40% of sampled bacteria and 85% of sampled archaea have CRISPR–Cas systems. Often, these microbes can capture pieces of an invading virus's genome and store the sequences in a region of their own genome, called a CRISPR array. These arrays then serve as templates to generate RNAs that direct CRISPR-associated (Cas) enzymes to cut the corresponding DNA. This can allow microbes carrying the array to slice up the viral genome and potentially stop viral infections.

Viruses sometimes pick up snippets of their hosts' genomes, and researchers had previously found isolated examples of CRISPR–Cas in viral genomes. Molecular biologist Jennifer Doudna and microbiologist Jillian Banfield at the University of California, Berkeley, and their colleagues decided to do a more comprehensive search for CRISPR–Cas systems in viruses that infect bacteria and archaea, known as phages. To their surprise, they found about 6,000 of them, including representatives of every known type of CRISPR–Cas system. "Evidence would suggest that these are systems that are useful to phages," says Doudna.



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Phages (red) might use CRISPR to compete.

The team found a wide range of variations on the usual CRISPR–Cas structure, and some of the viral Cas enzymes were remarkably small. This could offer a particular advantage for genome-editing applications, because smaller enzymes are easier to shuttle into cells. Doudna and her colleagues focused on a particular cluster of small Cas enzymes called Casλ, and found that some of them could be used to edit the genomes of lab-grown cells from thale cress (*Arabidopsis thaliana*) and wheat, as well as human kidney cells.

The results suggest that viral Cas enzymes could join a growing collection of gene-editing tools discovered in microbes.

In the meantime, researchers will continue to search for potential improvements to known CRISPR–Cas systems. Makarova anticipates that scientists will also be looking for CRISPR–Cas systems that have been picked up by plasmids — bits of DNA that can be transferred from microbe to microbe.

"Each year we have thousands of new genomes becoming available, and some of them are from very distinct environments," she says. "So it's really going to be interesting."