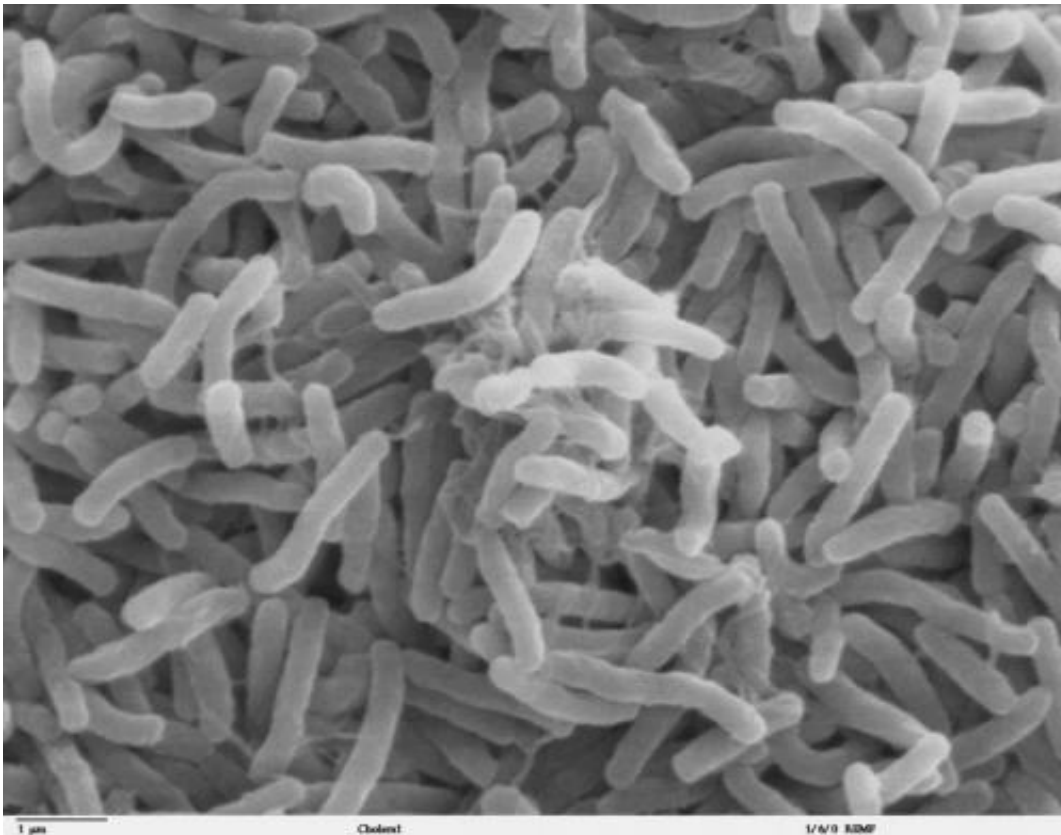


# Cocktail of bacteria-killing viruses prevents cholera infection in animal models

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Scanning electron microscope image of *Vibrio cholerae* bacteria, which infect the digestive system. Credit: Ronald Taylor, Tom Kirn, Louisa Howard/Wikipedia

Oral administration of a cocktail of three viruses, all of which specifically kill cholera bacteria, prevents infection and cholera-like

symptoms in animal model experiments, report scientists from Tufts University School of Medicine (TUSM) and the Sackler School of Graduate Biomedical Sciences at Tufts in *Nature Communications* on Feb. 1. The findings are the first to demonstrate the potential efficacy of bacteria-killing viruses—known as bacteriophages, or phages—as an orally administered preventive therapy against an acute gastrointestinal bacterial disease.

"While phage therapy has existed for decades, our study is proof-of-principle that it can be used to protect against infection and intervene in the transmission of disease," said senior study author Andrew Camilli, Ph.D., Howard Hughes Medical Institute Investigator and professor of molecular biology and microbiology at TUSM. "We are hopeful that [phages](#) can someday be a tool in the public health arsenal that helps decrease the global burden of cholera, which affects up to four million people around the world each year."

In previous work, Camilli and colleagues searched for phages that are specific for *Vibrio cholerae*, the bacterium that causes cholera—a potentially lethal infectious disease marked by severe diarrhea and dehydration. While phages that kill *V. cholerae* are abundant in nature, the team identified three strains that uniquely retained the ability to kill *V. cholerae* within the small intestine, the site of infection in humans. These phages function by targeting bacterial surface receptors normally involved in infectiousness, making them ideal therapeutic candidates—to develop resistance, cholera [bacteria](#) must acquire mutations in these receptors, which cause the bacteria to become less infectious.

## Prevent and protect

In the current study, a team comprised of Camilli, Minmin Yen, Ph.D., recent graduate of the Molecular Microbiology Program at the Sackler School, and postdoctoral fellow Lynne Cairns, Ph.D., carried out a series

of experiments in small animal models of cholera to test the efficacy of these phages as a preventative treatment. Animals were given an oral dose of a cocktail containing all three phages, at time points ranging from three to 24 hours before infection with a standardized amount of *V. cholerae* bacteria.

A preventative dose of the phage cocktail eliminated *V. cholerae* in the small intestines of over half of treated animals when given three hours before infection. In remaining animals, and for those treated up to 24 hours before infection, bacteria numbers were reduced 500-fold or more on average, compared to untreated controls. Overall, treatment was most effective in reducing bacterial load when given between three and 12 hours before infection.

The team found no evidence of cholera-like diarrhea and no significant weight loss in treated animals.

To study bacterial resistance, one of the historical obstacles to the use of phages as a therapy, the researchers isolated *V. cholerae* that survived treatment and conducted whole-genome and molecular analyses. While some bacteria acquired resistance against one or two of the phages, no bacteria were resistant to all three phages in the cocktail. As expected based on previous work, surviving bacteria that developed phage resistance had mutations in key protein receptors that rendered the bacteria avirulent and unable to cause infection.

"It took almost a decade of work, from our lab and collaborators around the world, to identify these phages, understand their life cycle, reveal the underlying biology and mechanisms by which they attack cholera and show how resistance develops," said lead study author Minmin Yen, who conducted this research as part of her graduate thesis and is now a postdoctoral fellow in the Camilli lab. "By building on that work, we are now able to demonstrate that these phages can be effective at protecting

against cholera and that the bacteria do not develop resistance to the phage cocktail."

## Filling a treatment gap

Discovered roughly a century ago, bacteriophages have remained relatively unexplored in Western medicine as a therapy due to the prevalence of antibiotics. However, the dramatic rise of antibiotic-resistant bacteria has led to renewed interest in [phage therapy](#), which can target specific strains of harmful bacteria while leaving host cells and [beneficial bacteria](#) unaffected.

Carried by contaminated water, cholera spreads quickly through communities during outbreaks. A primary path of transmission is from infected individuals to other household members, a process that typically occurs within one to two days. The research team envisions the phage cocktail as a rapid-acting preventative oral medication that can be repeatedly taken during this critical window. Reducing household transmission when an outbreak begins would help slow the spread of cholera and lessen the impact of the disease on communities.

With animal model experiments established, Camilli's team and collaborators are now exploring human clinical trials. Phage therapy has a well-established safety profile in humans, based on decades of use in eastern European countries such as Georgia. In addition, phages are the most abundant organism on Earth, and humans are continuously exposed to them with no harm. The team is also investigating the production of phages at scale, and believes that it can be done economically and priced appropriately for use in the developing world. They recently formed a company—PhagePro, which received seed funding as a winner in the Tufts 100K New Ventures Competition—to further test and develop their phage cocktail. Tufts University has filed a related patent application.

If successful, their efforts could lead to an important tool for public health professionals. A cholera vaccine exists and is recommended by the World Health Organization, but needs to be given at least two weeks in advance to be effective. Rehydration therapy is the standard treatment for cholera, but clean water is typically hard to come by during an outbreak. Antibiotics are effective at eliminating [cholera bacteria](#), but they contribute to the spread of antibiotic-resistant strains and can harm beneficial bacteria such as those in the large intestine.

"A preventative phage treatment is unlikely to eradicate cholera, but we think that it could fill an important gap in treatment, which is immediate protection against transmission in households," said Camilli, who is also faculty in the Molecular Microbiology Program at the Sackler School. "Additional work needs to be done, particularly a deeper understanding of phage biology while inside the gastrointestinal system, but if we are able to confirm its safety profile and efficacy in humans, it has the potential to be the best option for many communities affected by cholera."

**More information:** Minmin Yen et al, A cocktail of three virulent bacteriophages prevents *Vibrio cholerae* infection in animal models, *Nature Communications* (2017). [DOI: 10.1038/ncomms14187](https://doi.org/10.1038/ncomms14187)

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