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NEWS

‘Gazillions’ of viruses, called phages, are our hope when antibiotics fail, Yale biologist says

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Mark Smith, father of Mallory Smith, collects phages at the New Haven sewage-treatment plant.

Diane Shader Smith / Contributed photo

NEW HAVEN — It’s the worldwide health care crisis that has been growing since before the COVID-19 pandemic, but researchers at Yale University and a few other places are hard at work to find cures.

It’s the problem of antibiotic-resistant bacteria, often called superbugs. The common infections and bacterial diseases that can’t be cured with any available antibiotics are growing, threatening life and limb.

The answers are all around us, in trillions of viruses known as bacteriophages or, as they are more commonly called, phages. They are not harmful to humans, but they attack bacteria, both killing them and reducing their resistance to antibiotics.

“People know cancer is a big deal, because either they faced it themselves or they’ve had a family member or some close friend deal with it,” said Paul Turner, an evolutionary biologist and director of the Yale Center for Phage Biology and Therapy, which officially launched last week.

“That’s where this is headed … if the projection is true, which I do believe it’s true, that more people will be dying from antibiotic-resistant superbugs than they will from cancer annually.”

According to a study in the Lancet medical journal this month, there were 1.27 million deaths worldwide caused by antibacterial-resistant infections in 2019. The Centers for Disease Control and Prevention reports that more than 2.8 million such infections occur in the United States each year, with 35,000 people dying from them.

“The antibiotic-resistance crisis, the looming pandemic, is already here,” Turner said. “It’s just not so acute that it plays on the news much and that you hear about it enough and the problem is, once it turns the corner, which it will, to cause this high degree of mortality, then it will get more press but now is the time to figure out the alternatives like phage therapy.”

The issue received more publicity recently when a documentary about Mallory Smith, who died of cystic fibrosis before phages potentially could have saved her life, premiered in New York and Los Angeles. “Salt in My Soul” is also available to stream.

The diseases caused by antibiotic-resistant bacteria are not uncommon ones, either. They include MRSA, gonorrhea, pneumonia, tuberculosis and Clostridioides difficile, or C. diff., which alone accounts for 12,800 deaths per year. Many can be picked up during hospital stays. Not all strains of these diseases are resistant to every antibiotic, but the number of antibiotics that will cure them is decreasing, Turner said.

“This is what’s getting scary,” he said. In 2017, the World Health Organization listed the six most concerning bacteria. “The ones that were on the list are not obscure bacteria. … They’re very recognizable bacteria,” Turner said.

Some have become "what's defined as pan-drug resistant," he said. "They are already resistant to all currently approved antibiotics. ... Part of the issue is, there's really not much money in Big Pharma to discover antibiotics anymore. They sit on a shelf."

That's because doctors are concerned that bacteria will become resistant to the new antibiotic, so it becomes "a last-resort drug," Turner said. Doctors will say, "'I'm going to put it on the shelf and we're going to use it if all these other ones fail, and it ends up not recouping the money.' And Big Pharma said, 'We're out. We're not going to do it,'" he said.

The problem is all around us. "It's already bad enough that certainly here in New Haven, places like Hartford ... the physicians already see cases of patients for which currently approved antibiotics just don't work," Turner said.

He said about five years ago, a surgeon told him how "even in the Greater New Haven area, how many people are suffering with antibiotic-resistant bacterial infections that threaten their limbs and they might be headed for removal of those limbs as the obvious course of action. It was quite shocking to me because that was one of the earliest advancements of phage therapy, is you can save somebody's foot from having to be amputated."

The limbs are vulnerable because if blood circulation is reduced because of diabetes or another disease, the body's immune system can't fight off the infection as well.

In Yale's first case, a patient had an infection, which started on a mesh covering an artificial aortic arch. Turner said the patient's doctor told him, "This guy is remarkably alive. His sternum has been eroded away because of the chronic infection that is on his artificial part of his heart and it's out of control. And I'm telling you, I'm looking you in the eye ... I'm surprised this man is alive. He really has no other options. He's too elderly for us to go in and take the infested part out and put it back in and expect him to actually survive the surgery."

Turner's colleague Ben Chan created a phage suspension that killed the infection. The phage came from Dodge Pond in East Lyme. The man survived and "the rest is history," Turner said.

What makes phages especially valuable is that they not only kill the bacteria, but they make the pathogen evolve so that they become resistant to the phage, but vulnerable to antibiotics again.

“The vast majority of bacteria that cause problems in human medicine are what are called opportunistic pathogens,” Turner said. “They don’t have to be in your body, they could be living in soil, they could be living in some other animal.” If the body is no longer a welcoming place for them, they’ll go into some other environment.

As an example, Turner described how some bacteria have structures called efflux pumps. “So what efflux pumps do is, if an antibiotic gets in, it pumps it out,” he said, increasing its resistance to antibiotics.

“And now they’re known to function so well that you get these multi-drug and pan-drug superbugs. The idea we had is, I’m going to go find a phage that interacts with efflux pumps as the way that it bonds,” he said. “The phage is going to kill the bacteria, but what’s happening is that the bacteria are not going to sit around and just die, die and die.” Instead they will evolve to become resistant to the phage.

The best way for the bacteria to evolve is to “just ditch the efflux pump,” Turner said. “It’s like the easiest path to removing the problem. And guess what, that makes them antibiotic sensitive and then we throw the antibiotic in, it kills the bacteria, problem solved.”

Turner and Chan favor this method of “finding the right phage” for each problem, trying to make the technology “more foolproof. That’s our angle.”

Other centers, such as the University of California at San Diego, Baylor College of Medicine, Texas A&M and the Mayo Clinic, the other main players, are “not characterizing individual phages,” Turner said. They tend to use cocktails of many phages, which do the job but, according to Turner, don’t advance the science.

Phages were discovered about the same time as antibiotics, and Western medicine went with the broad-spectrum antibiotics that killed most disease-causing bacteria. But in Eastern Europe, Chan has said, phages are used much more commonly, and he has gone to Haiti and the Democratic Republic of Congo to seek out phages that will kill cholera, which is endemic in those countries.

“Currently, the state of the art is you think you need to go to the place where it’s worse,” Turner said. But while Vibrio cholerae causes cholera, “there are relatives of Vibrio cholerae that live in Long Island Sound, other Vibrios,” he said. “So you could look in Long Island Sound for phages against that bacteria that might just work against cholera bacteria.

“The most biodiverse thing on this planet are phages,” Turner said. “To the point of, in my backyard, in a gram of soil, I’m going to find gazillions of them that have probably never been described in the literature.”

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