THE NATURAL SUPERBUG CURE

No One Is Telling You About

Deadly antibiotic-resistant infections have American doctors trembling. Thanks to a therapy long forgotten here, one country in Eastern Europe is having no such crisis. So why are thousands of us dying?

BY KOREN WETMORE

COURTESY OF THE ELIAVA INSTITUTE

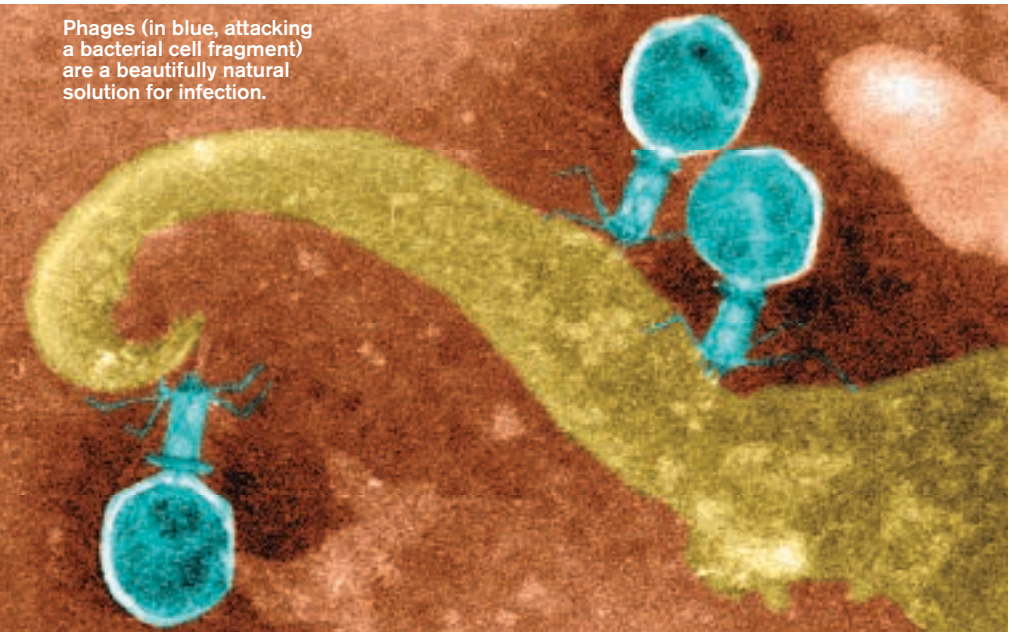
In Tbilisi, Georgia, scientists have been killing MRSA and *E. coli* without antibiotics for decades.

Laura Roberts clutched her Bible in her lap and gazed out the plane window at the wispy clouds below. She turned to her brother, Andrew, seated beside her, and smiled, not wanting to worry him. She was thankful to have him there and deeply moved by his willingness to accompany her on this uncertain journey.

Fighting back nausea and the throbbing pain permeating her body, Roberts, a vivacious single mom with an open face and warm, dark eyes, prayed for the strength to make it through the next 23 hours. She'd take three long flights from her home in Fort Worth, TX, before reaching her destination—and the unconventional treatment she hoped would save her life.

Doctors had told Roberts she had 3 months left to live, at best—not because she had terminal cancer or some exotic virus, but simply because she had developed a sinus infection that antibiotics could not cure.

More than 2 million Americans each year get sick from antibiotic-resistant bacteria, which find their victims both in the hospital and in the everyday world. At least 23,000 die annually from those infections. A report released last spring by the World Health Organization suggests that those numbers are about to get much higher. The WHO warns of an approaching "postantibiotic era," a time when common infections (strep throat) and minor injuries (a scraped knee) can kill.



Phages (in blue, attacking a bacterial cell fragment) are a beautifully natural solution for infection.

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"Roberts had 3 months to live—not because she had terminal cancer or some exotic virus, but simply because she had developed a sinus infection that antibiotics could not cure."

For Roberts, that dystopian future had already arrived. Like millions of other allergy sufferers nationwide, she had relied on antibiotics to fight the infections that often followed the seasonal swelling of her nasal passages. But then she got a staph infection caused by the infamous methicillin-resistant *Staphylococcus aureus*. In the 7 years that followed, she and her doctors battled the microbes, but MRSA spread from her sinuses to her ears, lungs, and stomach. Eventually, there wasn't an antibiotic left that could help her. The infections became chronic and ravaged her body, depleting her strong frame; poor circulation turned her limbs stiff and cold. She found herself flattened by nausea and pain as she faded further each day.

Last-resort doctors she saw at the Mayo Clinic finally told her there was nothing more they could do. At age 51, she would have a few months left to say good-bye to her two daughters and, perhaps, spend one more holiday season with her family. "When I was told to get my affairs in order, it hit me like a ton of bricks," Roberts says.

That was the impetus she needed to drag her exhausted body through the long journey to the Phage Therapy Center in Tbilisi, Georgia. She had hung her hopes on what appeared to her American doctors to be a long shot, one she'd heard about on TV, no less: bacteriophage therapy, a treatment used widely in Eastern Europe in place of antibiotics to kill infections. "I didn't know if it could help me, but if I was going to die, I was going to die fighting," Roberts says.

Bacteriophages ("bacteria eaters"), commonly called phages, are viruses that infect bacteria but not humans. Found in water, soil, and even your digestive tract, phages dwell wherever bacteria are found because they rely on them to reproduce. They drill through a bacterium's surface, hijack its DNA, and then replicate themselves within it until the cell bursts. Cocktails of phage viruses can kill a bacterial infection in the human body with remarkable accuracy, taking out only the infiltrators and leaving important populations of "good" bacteria intact—unlike the blunt tool of antibiotics, which tend to wipe out

KILLER *E. COLI*, MEET YOUR MATCH

These spaceship-shaped viruses are capable of demolishing infections like *E. coli* and MRSA that would otherwise kill. Here are the basics.

A BACTERIOPHAGE is a virus that kills bacteria (*phage* is Greek for "to eat"). The viruses are found in soil, water, and everywhere else bacteria thrive.

THERE ARE COUNTLESS TYPES of phages in nature. Each fixates on a particular bacteria: Phages that prey on *E. coli* cells, as these do, won't attack "good" *Lactobacillus* bugs alongside them. That's good news for humans.

THIS ISN'T AN ALIEN LANDING but, rather, a cohort of phages attacking an *E. coli* cell. They'll drill into its surface, take over its DNA, and replicate until the cell bursts. Harsh but effective.

MODERN TOOLS allow scientists to avoid using a harmful type of phage that shares its DNA with bacteria instead of killing them, making an infection worse, not better.

LEE D. SIMON/GETTY IMAGES, SCIENCE PICTURE CO./GETTY IMAGES (INSET)

a wide swath of good bugs and bad.

According to experts abroad and in the US, phages are one of the most promising solutions to our growing problem of resistant bacteria. "We badly need new antimicrobial treatments, but there aren't that many coming down the pipeline," says synthetic biologist Timothy Lu, associate professor of biological engineering at MIT. "Bacteriophages are a largely untapped resource for that."

You've likely never heard of phages, and since they're not approved by the FDA, there's a good chance your doctor's understanding of them is limited or out-of-date. So if, say, tomorrow you were to join the hundreds of thousands of Americans whose sinuses or digestive tracts or skin cells have been invaded by drug-resistant infections—if tomorrow you found yourself tumbling down a medical rabbit hole of specialists and prescriptions that ultimately couldn't keep you safe from the bacteria ravaging your insides—well, you'd be told you were out of luck, the way Roberts was. You'd be destined for illness and possibly death at the mercy of these invaders.

So far, the Sisyphean American solution to this crisis has been to create more antibiotics, which inevitably lose their potency as the bacteria they're meant to kill mutate and multiply. Even more surreal, a therapy that's been working for a century

in a few poor countries on the other side of the world could save many of the thousands of us who die annually in this quiet crisis. "Phages have been used in places like Poland and Russia for decades with success—it's become standard therapy," says microbiologist Cliff Snyder, who works on phages for the US Army Medical Research and Materiel Command. Drug resistance poses few problems in Georgia, a nation of nearly 5 million, where phage therapy is standard protocol. In Poland, where antibiotics are common, phages are put to use when those drugs fail.

Inspired by this Eastern European success outsmarting MRSA and other killer infections, Snyder and his team are working with the Walter Reed Army Institute of Research and the pharmaceutical company AmpliPhi Biosciences to get phage therapies through the multiple stages of testing and approval required in the US.

> **I don't want it to reach the level of Ebola, where we can't treat people on a large scale.**

"We're confident in the potential," Snyder says. "But people need to understand that bacteriophage products have to be tested, the production methods have to be standardized, and they must satisfy the FDA. That isn't cheap, easy, or quick."

Some experts estimate that phages will be more widely used here in the next 5 to 10 years. Others are gunning to get compassionate-use phage therapy set up much sooner, the way unapproved treatments were used on Ebola patients in the US last fall. In the meantime, there's a legal but circuitous route out of the drug-resistance rabbit hole if you live in the US. You are now one of the lucky few who know what it is and what to do.

In the 3 years leading up to Roberts's plane trip, MRSA infections tore through her body with increasing intensity. Her bed felt like a tomb, yet with so little strength left, she had no choice but to rest. She left home only for weekly appointments to have her sinuses and ears drained. She would try to eat—a scrambled egg, a piece of toast—but little would remain in her stomach before she retched it up. She laughed sometimes at what a spectacle she must be, clutching an IV pole and administering her own drugs—whatever new antibiotics the doctors were trying—through a line in her arm morning, noon, and night. If not for the constant nausea, she might have been able to call that living. But it wasn't living. It was mere existence.

Her family offered help, but Roberts insisted on driving herself to doctors'

Scientists at the Phage Therapy Center identify phages for each patient's particular infection.

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visits. It was hard to breathe, and the pain was excruciating. "Lord, get me there, please," she pleaded each time she got behind the wheel.

When the day came to travel to Tbilisi, prayer was all she had. "She looked frail and pale and had to use a walker," says Andrew, who flew from his home in Vermont to join his sister for the trip. "It felt like a gamble, traveling across the world for help when we weren't sure what was going to happen."

Two weeks before the trip, Roberts submitted swab samples of fluid from her sinuses and ears to the Phage Therapy Center, an American-owned organization that connects patients here in the US with scientists in Georgia who customize phage cocktails for the infections. Roberts's samples revealed three MRSA strains. The consulting doctor recommended that she book an immediate flight to Tbilisi and 3 weeks of treatment at the center. For patients with simpler cases, the center ships patients at-home treatments of targeted phage drops, drinks, or powders (see next page). This is legal through the FDA's personal importation policies.

In Tbilisi, Roberts and her brother met with Zemphira Alavidze, a scientist who runs the center's therapy lab. A kind-looking woman in her 60s with lush, dark-brown hair reaching her shoulders, Alavidze interviewed Roberts about her medical history. Roberts pulled out a duffel bag full of

prescriptions and noted the surprised expression on the doctor's face.

For hours each day, medical staff cleaned and cleared Roberts's nasal passages and ears and inserted long metal instruments wrapped in phage-soaked gauze deep into her sinuses. It felt like they almost touched her brain, but, oddly, they never hurt. Doctors put phage drops in her nose and powders in her ears. Each night, back in their hotel room, Andrew placed more drops in her nose and ears, and she drank a bottle of phage preparation to treat the infection in her stomach. Clear, tasteless, and odorless, the liquid slid down her throat and, to her surprise, stayed put, as did the piece of chicken and bit of salad and rice she ate the first night in Tbilisi.

Soon her circulation improved and her hands and feet grew rosy and warm. By the third week of treatment, her breathing and energy had returned to normal, and all pain was gone. Roberts left the hotel for walks, tours of the city's architecture, and dinners out. "It blew my mind that we arrived in one condition and by the last week, we had become tourists," her brother says. "We came with that walker; when we left, we didn't even bring it with us."

Back in Texas, Roberts visited her ear, nose, and throat doctor, Natalie Roberge, to show her the treatment results. Her physician since 1996, Roberge had noted Roberts's condition just prior to the Tbilisi trip and could barely believe her eyes when she saw her patient again. "Beforehand she had that thick goo in her ears, and her sinuses were filled with polyps," Roberge says. "When she came back, the lining of her middle ear was very normal and healthy looking. Her nose and sinuses were normal. No more polyps, no unusual drainage. It was really striking—there was such a change in her."

Phages had completely cured the infection—which involved three different MRSA strains and caused 7 years of suffering—within 3 weeks of treatment. "It's a shame that you have to fly to Georgia to save your life," Roberts says. "It's a shame phages are not available in the US. I hope that happens in my lifetime, but I'm not sure it will."

GOT MRSA?

HIDDEN TIP: YOU CAN TRY PHAGES.

Patients with a resistant infection can access phages without leaving the US, depending on the infection and its severity.

HERE'S HOW IT WORKS.

PATIENTS REGISTER AT PHAGETHERAPYCENTER.COM and describe their problem, then send along medical records and a bacterial sample—stool, urine, or a swab.

THE SAMPLE IS TESTED to see whether the infection is one that can be treated with a phage preparation.

ONCE THE BACTERIA are identified and the correct phage or phage combination is isolated, a Phage Therapy Center doctor prescribes a treatment that is prepared in Tbilisi, Georgia, and then shipped to the patient's home. Phages generally come in liquid form and are applied topically, inserted as drops, or taken orally.

IN SEVERE CASES, particularly with chronic conditions like Laura Roberts's, patients travel to Eastern Europe for more extensive treatment.

COSTS RANGE FROM $800 for a home-delivered preparation to $6,000 or more for treatment abroad. Roberts's cost was about $12,000, including travel. Some insurers cover a portion of the costs; others, nothing at all.

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Phages are tested on a dish of growing bacteria. The clear areas are where the bugs have been killed.

Why are US doctors and pharmaceutical companies in standby mode and phages still unused while more people die every year? There's no single, satisfying answer, but ask a phage-savvy scientist and here's what you'll hear: Phages are expensive to test because they don't adhere to the Western "one size fits all" treatment paradigm. Rather, they are custom remedies made from naturally occurring viruses, applied in ways specific to the particular strains of bacteria each patient is suffering from. It'll take leaps of time and technology to turn them into prescription drugs.

To get phages approved in the US, a drug company would have to test not only each individual phage but also all combinations of phage cocktails (of which there are a near-endless variety), and then prove their safety and efficacy in multiphase human trials.

While dozens of Eastern European studies in adults and children with infections have shown success with phage therapy, the one completed US study in humans pitted a single cocktail against a variety of infections and, predictably, didn't show impressive results. Even if a phage cocktail gets traction in US drug development, it will face an uphill trek.

"Phase 2 and 3 studies, where you need data from hundreds of people, take a long time," Snyder says. "We have to gather the patients, put them through the study protocol, and do this in a very well-documented, controlled way. But it's the only way in the Western world we get answers we can trust."

Still, scientists are quietly pursuing such studies. In its 2014 strategic plan to combat resistant microbes, the National Institute of Allergy and Infectious Diseases named phage therapy one of seven leading programs to pursue—and the only one that has already been tested in humans. Last fall, health-care facilities in France, Belgium, and Switzerland began recruiting patients for a $6.2 million study in which phages treat people with drug-resistant infections from burn wounds. Researchers around the world have found phages that attack and destroy 85% of the MRSA strains they've encountered. The US Army has launched a sizable program developing phage cocktails to fight one of our deadliest bacteria—*Staphylococcus aureus*—and hopes to expand to other deadly infections caused by pathogens such as *E. coli* and *Pseudomonas aeruginosa*.

The realistic goal in the US, says MIT's Lu, should be not to import the artful Eastern European phage therapy but, rather, to incorporate phages into existing treatment methods. Because antibiotics are so entrenched here, phages need to be part of the arsenal, accompanying the drugs and enhancing their effects rather than replacing the meds altogether. "In the short term," he says, "that will plug more easily into the current way people practice medicine."

To get away from naturally occurring phages, which are highly diverse and can't be patented, Lu and his team are working on "engineered" phages that are more uniform and consequently more compatible with drug regulations. These are tweaked enough to be patentable and possibly more appealing to a pharmaceutical company that wants to protect an investment of potentially millions of dollars in product development. "I hope that within 5 years, we may see early approvals or increasing numbers of clinical trials in the Western world using phages," Lu says.

None of this helps with the question of what 2 million suffering Americans should do now or in 5 years, if Lu proves too optimistic. Some researchers call for major hospitals to set up phage banks for compassionate use in patients whose infections resist antibiotics. "Someone who is about to die of a MRSA infection could be given an injection with a phage cocktail that could be a lifesaver," says virologist Ryland Young, director of the Center for Phage Technology at Texas A&M University. "It is within the power of the medical community to do this. If there was enough of a public groundswell, the FDA could convene a panel and come up with a way to treat phages differently from new chemical drugs."

> **It will take leaps of time and technology to turn phages into US prescription drugs.**

But the scourge of resistant bacteria is an epidemic without a trademark ribbon or a walkathon in its name, a chilling crisis that's been intensifying for years but thus far has elicited no real public outcry. "No one thinks it's a big deal, because it hasn't affected them yet," says Jason Newland, a practicing MD and a member of the Infectious Diseases Society of America's antimicrobial resistance committee. "We need to educate folks that this situation is going to change medicine, so that people will start asking the FDA to develop regulations that are not nearly as stringent. I don't want it to reach the point of Ebola, where we have nothing to treat people on a large scale."

For Roberts, the gamble of a long journey to Georgia turned out to be lifesaving. Now 61, she still battles seasonal allergies, but the MRSA is gone. Should another infection arise, she says she will gladly use phages to treat it. "The difference is like night and day," she says. "I'm enjoying life again. Even today, I run into people who don't recognize me—and I'm sure a lot of them thought I had passed on. But no, I'm still here."