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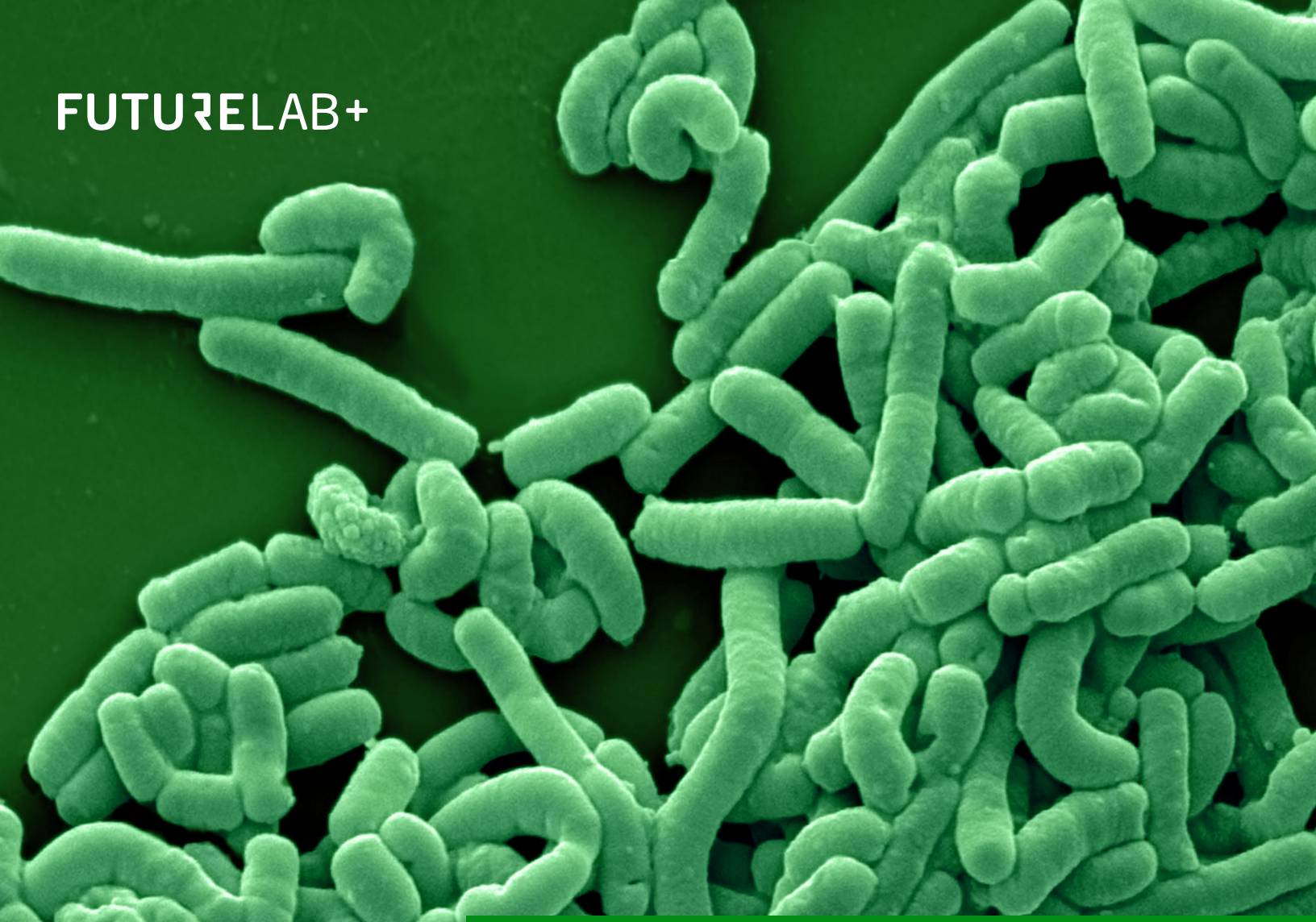


AG/ENVIRONMENTAL

Solution Seeking Microbes

Antibiotics, Resistance, and Combating Disease

Developed in partnership with:

Discovery Education and Ignited

In this Lesson Plan:

Print the **Teacher Section** →

Medical technicians working on bacterial culture and drug resistance of pathogens in a laboratory.

—

Cover Image
Lactobacillus casei is one of many friendly bacteria in your gut microbiome.

Print the **Student Section** →

This document is separated into two sections, For Teachers [T] *and* Student Resources [S]*, which can be printed independently.*

Select the appropriate printer icon above to print either section in its entirety.

Follow the tips below in the Range field of your Print panel to print single pages or page ranges:

Single Pages (use a comma): T3, T6

Page Range (use a hyphen): T3–T6

AG/ENVIRONMENTAL / SOLUTION SEEKING MICROBES

Antibiotics, Resistance, and Combating Disease

DRIVING QUESTION

How are new treatments and therapies safely tested on humans?

OVERVIEW

According to the World Health Organization (WHO), antibiotic resistance is the greatest threat to human health, food security, and economic development. It is estimated that treating cases of antibiotic-resistant bacteria costs an average of $22 billion annually. Up to half of antibiotic treatments are deemed unnecessary, and nearly 23,000 patients are dying from antibiotic-resistant bacterial infections. How does antibiotic resistance happen? How can we develop and safely test new treatments and therapies in clinical trials that can be used concurrently with, or in place of, antibiotics?

In this lesson, students will investigate these so-called "superbugs," which are bacteria that have become resistant to most antibiotics. While learning about superbugs, students will understand the role of improper use of antibiotics in the emergence of antibiotic-resistant bacteria. Students will then learn about phage therapy as a potential next step in attacking superbugs. In the end, students will analyze a proposed clinical trial and determine if it is safe for a patient to participate in this clinical trial, taking into consideration the risks and benefits. Students will point out where concerns or clarifications are needed in the clinical trial.

ACTIVITY DURATION

Three class sessions
(45 minutes each)

ESSENTIAL QUESTIONS

How does antibiotic resistance arise?

What are bacteriophages and how might they be used to combat antibiotic resistance?

How are clinical trials designed so new treatments and therapies can be tested with minimal risk to patients?

OBJECTIVES

Students will be able to:

Understand the basic phage life cycle.

Identify how antibiotic resistance arises.

Explain how bacteriophages and antibiotics can be used in combination to combat superbugs.

Analyze a clinical trial to determine if the trial is deemed safe for patients.

BACKGROUND INFORMATION

Phage 101 from UCSD might be a helpful resource to teachers, as it explains bacteriophages in nature, the history of phage therapy, as well as the benefits, risks, and the future of phage therapy.

Materials

- **Antibiotic Resistance Simulation Capture Sheet**
- **When the Virus is the Cure Capture Sheet**
- **Clinical Trials Gone Wrong Reading**
- **Phage Therapy Clinical Trial Overview**
- **Clinical Trials for a New Phage Therapy Capture Sheet**
- **Career Profile: Ariangela J. Kozik, PhD**
- **Toolkit**

Pedagogical Framing

Instructional materials are designed to meet national education and industry standards to focus on in-demand skills needed across the full product development life cycle—from molecule to medicine—which will also expose students and educators to the breadth of education and career pathways across biotechnology.

Through this collection, educators are equipped with strategies to engage students from diverse racial, ethnic, and cultural groups, providing them with quality, equitable, and liberating educational experiences that validate and affirm student identity.

Units are designed to be problem-based and focus on workforce skill development to empower students with the knowledge and tools to be the change in reducing health disparities in communities.

SOCIAL-EMOTIONAL LEARNING

Students will learn about the many types of risks incurred by patients undergoing clinical trials, and hopefully empathize with the desperate situations in which these patients often find themselves. Students will consider ethical standards and safety concerns, and evaluate the benefits and consequences of clinical trials. Students will recognize how critical thinking skills are useful in a medical setting, where there is no perfect answer and lives are at stake. They will reflect on their role to promote personal, family, and community well-being.

CULTURALLY AND LINGUISTICALLY RESPONSIVE INSTRUCTION

Students will tackle real-world issues while they reflect and ideate about how a more diverse patient group can be recruited into clinical trials.

ADVANCING INCLUSIVE RESEARCH

In this lesson, students will examine the importance of regulations that have been put in place to dictate the parameters to design clinical trials, and consider how this can help rebuild trust with groups that have been exploited by past research. In order to understand how new therapies impact humans, it is essential to include a diverse participant pool in clinical trials. Students will examine sources of bias that can enter into the design of clinical trials, and will explore ways to address these biases in order to ensure research is inclusive of people from more diverse backgrounds.

COMPUTATIONAL THINKING PRACTICES

As students examine the life cycle of a bacteriophage, they use the computational thinking strategy of decomposition to break the organism's existence into distinct stages. Decomposition is a useful skill that helps computer programmers "zoom in" and isolate specific sequences of code in order to solve problems. By "zooming in" on a specific phase of a bacteriophage's life cycle, students can pinpoint advantages and disadvantages to using phage therapy as an alternative to antibiotics.

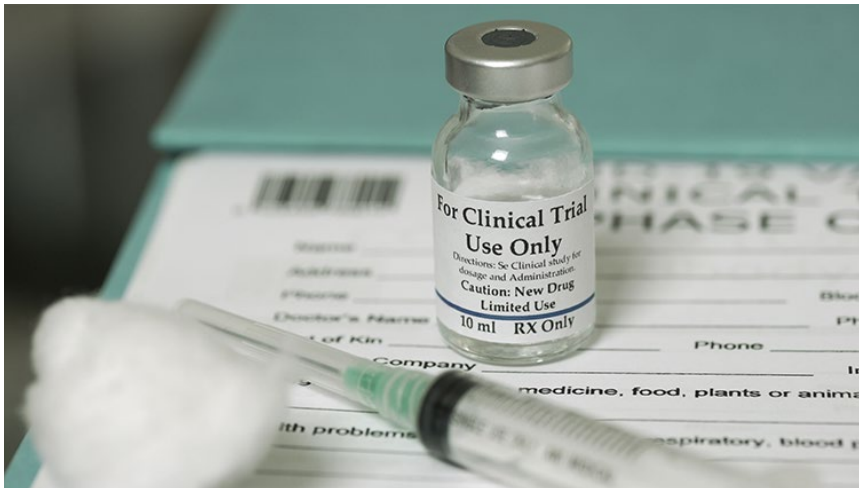
CONNECTION TO THE PRODUCT LIFE CYCLE

In this lesson, students explicitly learn about the drug development process in Day 2, and in Day 3 they create a clinical trial plan for a new phage therapy. The emphasis on treatment safety (and the earlier discussion of how phage therapy is a medical solution that avoids antibiotic resistance) connects to the **development** phase of the product life cycle.

Have you ever wondered…

How new treatments and therapies are safely tested on humans?

As we develop ways to combat diseases, proposed treatments and therapies need to be tested for safety before being released to the general public. This occurs after the **development** phase of the product development life cycle. Animal testing has been used to reduce risks for humans, but animal models can only partially predict human-drug interactions. Therefore, humans are still needed to fully assess the safety and efficacy of a potential new treatment or therapy. Although there are risks inherent to clinical trials, every day that we wait, more and more people suffer from diseases.



MAKE CONNECTIONS!

How does this connect to the larger unit storyline?

This lesson focuses heavily on solving health-related problems by using microbes. Although previous lessons have focused on superhero bacteria, this lesson shifts to highlight that some bacteria have negative effects and can be combated using microbes, including antibiotics and phage therapy. This lesson builds toward students analyzing a clinical trial, which would be an important step in any microbe-related solution to human health problems.

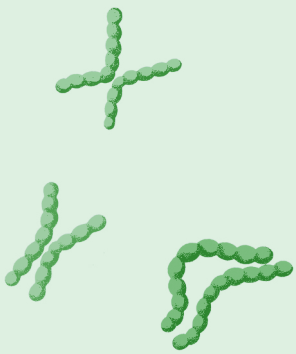
How does this connect to careers?

Clinical research coordinators work under the direction of a program director (often a PhD principal investigator) to execute the operations involved in testing treatments. The clinical research coordinator might enroll new patients, work with existing patients, record study data, ensure the study's legality, and even train other people involved in the clinical trial of a new drug or treatment.

Genentech Career Spotlight:
Greg Cosma, toxicology

How does this connect to our world?

In order to discover cures for the many health-related issues, scientists need to carefully design trials to make sure treatments and therapies are safe for the general population.



Day 1

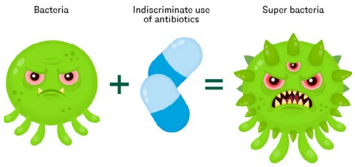
Procedure

LEARNING OUTCOMES

Students will be able to:

Explain why doctors prescribe antibiotics only when necessary.

Identify the importance of avoiding the creation of more antibiotic-resistant bacteria.



Whole Group (10 minutes)

1 Ask students if they have heard of superbugs. They may report that they have heard of them, know that they are very bad, and are aware that they can potentially cause severe disease. Play the video clip *How Sewage Saved My Husband's Life* (stop at 06:00). *Please review this video ahead of time to evaluate if this is an appropriate resource for your student audience. Strong language is included around minute six.*

2 Ask students if they learned anything more about what superbugs are. The video depicts bacteria that are resistant to antibiotics. You may wish to tie back to Lesson 1, where bacterial superheroes were studied. An analogy can be drawn to bacteria "crossing to the dark side" to become human enemies rather than friends as discussed with the microbiome in Lesson 1.

3 Conduct a Think/Pair/Share activity in which students discuss what they know about how antibiotics work. Have them also consider the question: *If bacteria become resistant to antibiotics, what capabilities would the bacteria need to be resistant to antibiotics?* (Students will most likely respond that they are "drugs" and that bacteria need a way to resist the drugs, potentially by developing mutations to the drug.)

Individual Work (35 minutes)

1 Introduce students to the *Contagion Simulation*. Tell students that the following activity simulates how bacteria become resistant to antibiotics and that they will observe the effect of antibiotics on bacterial growth by changing variables in the simulation. The *Antibiotic Resistance Simulation Instructions* will guide students to explore the following:

- Antibiotic dosage amount
- How often a patient takes a dose (and how bacteria react)
- What happens when a patient skips a dose
- What happens when bacteria that became resistant to the antibiotic enter a new host/patient

2 After completing the simulation, recording their answers on the *Antibiotic Resistance Simulation Capture Sheet*, tell students to reflect on the importance of using antibiotics appropriately by completing a CER about why patients should take their prescription accurately as prescribed.

Teacher Note > *Optional extension to discuss how antibiotics work. What is an antibiotic? is a good resource for students.*

Day 2

Procedure

LEARNING OUTCOMES

Students will be able to:

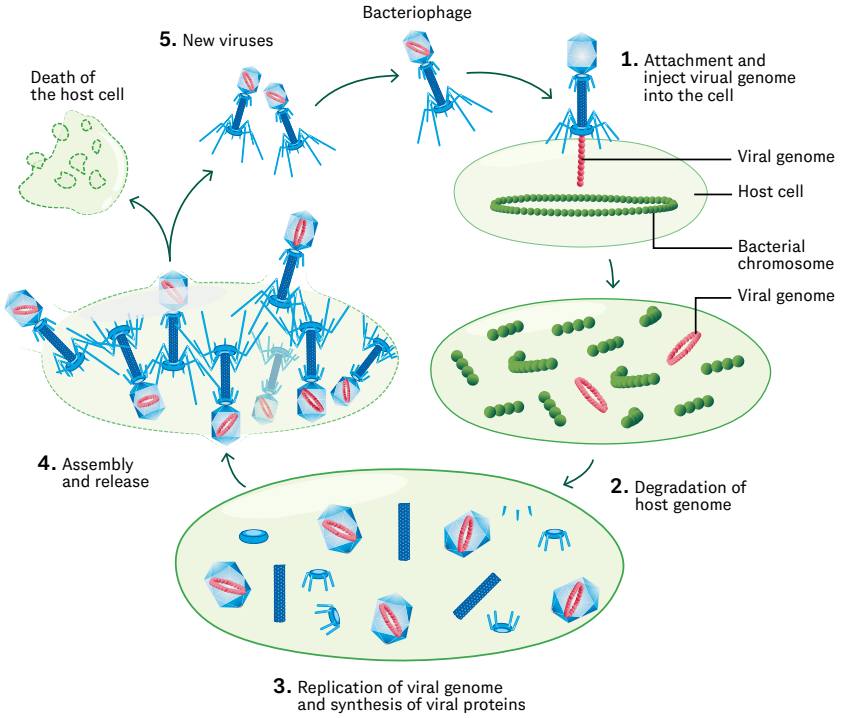
Describe the steps of the drug development process.

Explain the mechanism and **identify** benefits of phage therapy.

Small Group (15 minutes)

1 Ask students to discuss with a partner what the following statement might mean: The enemy of my enemy is my friend. ("The enemy of my enemy is my friend" is an ancient proverb, which suggests that two parties can or should work together against a common enemy.) How might this apply to fighting superbugs with something other than antibiotics? What is the enemy of bacteria? Students might think back to Lesson 1 where bacteria developed a shield or weapon (overcoming adversity). Remind them that bacteriophages are viruses that infect bacteria. How could bacteriophages be "the enemy of my enemy" in this situation? If students struggle to make this connection, a video or image of the phage life cycle can be shown as seen below:

Life Cycle of Bacteriophage



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Day 2

Continued

Procedure

2	Show students the description of *phage therapy* (07:00) from University of California San Diego School of Medicine. After reviewing, have them consider the topics below. Have students first discuss with their partners. After partner discussions, review each topic with the class. • Describe how phage therapy works. • Explain the benefits of phage therapy. • Discuss why phage therapy is considered safe.
3	Ask students to Think-Pair-Share what steps must be taken before this therapy could be given to humans (remind them of the model used in Lesson 2 to connect the microbiome with colon cancer). Students should respond that this should be tested on a non-human model first, such as mice. The next step would then be to test on a small group of people in what is called a clinical trial. Explain that students will now become more familiar with what this might look like for phage therapy.

Individual Work (20 min)

Tell students to read the article *When a Virus is the Cure* by the New Yorker, provided in the *When a Virus is the Cure Capture Sheet*. In it, they will answer questions as they read to understand phage therapy in better detail. Give students 20–25 minutes of class time to read this article, but let them know that if they need more time, they can finish the reading at home. They do not necessarily need to finish the article in class to move forward.

Teacher Note > *You may or may not wish to assign the article with questions. A shortened version with potential questions might be assigned as When a Virus is the Cure Capture Sheet. To further shorten the reading, you may wish to divide the class into seven groups and have each group answer a specific question, numbers 2 to 8, and have each group share important facts and vocabulary, and then answer their questions with the class.*

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Day 2

Continued

Procedure

Whole/Small Group (10 min)

1 Remind students that phage therapy is a relatively new procedure. Place the steps of the *Drug Development Process* on the board at random (Discovery and Development, Preclinical Research [using lab and animal models], Clinical Research [testing on humans to make sure the drug is safe], FDA Review [for approval for the general public], and FDA Safety Monitoring).

a. Give students two minutes to brainstorm with their partners, put the stages in order, and add a timeline to each stage (average time each stage might take).

b. List the steps in order (and include their general timing) so students can check to see if they got them right.

- Discovery and Development (3–5 years)
- Preclinical Research using lab and animal models (1–2 years)
- Clinical Research testing on humans to make sure the drug is safe (6–7 years)
- FDA review for approval for the general public (1–2 years)
- FDA Post-Market Safety Monitoring (indefinite)

c. Ask students where they think phage therapy research is right now. (Answers will vary, but they are in Preclinical stages as of 2021.)

d. Homework: Students will most likely need to finish the *When a Virus is the Cure Capture Sheet* after class hours.

Day 3

Procedure

LEARNING OUTCOMES

Students will be able to:

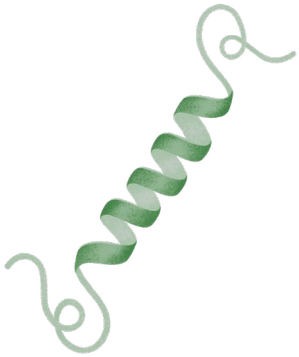
Analyze a clinical trial proposal and consider factors that maximize safety for patients.

Whole Group (5 minutes)

Ask students why it might be important to be cautious when designing new medicines and therapies when proposing to use them on humans. Remind them of the brainstorm they had on Day 2. It should be obvious that safety is a priority in order to mitigate as much risk as possible. It is also very important that the study and the safety procedures are communicated clearly to participants. Show examples from *Clinical Trials Gone Wrong Reading*. Discuss what might make a good clinical trial.

Small Group (25 minutes)

Recall the video from Day 1 that was paused at 06:00. Tell students they will be playing the role of Steffanie, Tom's wife, in deciding if she should enter him into a clinical trial. In groups, students should read the *Phage Therapy Clinical Trial Overview* and complete the *Clinical Trials for a New Phage Therapy Capture Sheet*.



Whole Group (15 minutes)

1	Tom's Outcome: Finish watching the *How Sewage Saved My Husband's Life* from a Superbug video. Relate how Tom, and other people like him, are the superheroes in discovering new treatments and therapies.
2	Allow students time to complete Lesson 3 questions on their **Toolkits**. Encourage students to ask questions or to volunteer their answers.
3	Invite students to read the scientist profile on *Ariangela Kozik*, focusing on what she does in her field and what might be most relatable or what resonates most with the students. They should log their thoughts in the **Toolkit**: *Based on the career profile in this lesson, what does this tell you about the types of people that do science? What did you find most relatable?* If time permits, you may ask students to share their thoughts.

National Standards

Next Generation Science Standards

LS4.B: Natural Selection
The traits that positively affect survival are more likely to be reproduced, and thus are more common in the population (HS-LS4-3).

Science and Engineering Practices

Analyzing and interpreting data
Analyze data using tools, technologies, and/or models (e.g., computational, mathematical) in order to make valid and reliable scientific claims or determine an optimal design solution.

Using mathematics and computational thinking
Use mathematical, computational, and/or algorithmic representations of phenomena or design solutions to describe and/or support claims and/or explanations.

Engaging in argument from evidence
Compare and evaluate competing arguments or design solutions in light of currently accepted explanations, new evidence, limitations (e.g., trade-offs), constraints, and ethical issues.

Career and Technical Education (CTE)

A2.0
Understand the ethical, moral, legal, and cultural issues related to the use of biotechnology research and product development.

A2.4
Understand the critical need for ethical policies and procedures for institutions engaged in biotechnology research and product development.

A2.5
Describe the dilemma of health care costs related to advancements in biotechnology and public access to treatments.

A5.1
Use the Internet and World Wide Web to collect and share scientific information.

A6.4
Create data tables and graphs using Excel for the purpose of collecting and analyzing data.

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National Standards

CTE *Continued*	**A7.2** Be aware of the role of agencies in promoting patient safety, quality control, and entrepreneurship.
	4.1 Use electronic reference materials to gather information and produce products and services.
	4.3 Use information and communication technologies to synthesize, summarize, compare, and contrast information from multiple sources.
	5.3 Use systems thinking to analyze how various components interact with each other to produce outcomes in a complex work environment.
	5.6 Read, interpret, and extract information from documents.
	7.4 Practice time management and efficiency to fulfill responsibilities.
	7.8 Explore issues of global significance and document the impact on the Health Science and Medical Technology sector.
	10.1 Interpret and explain terminology and practices specific to the Health Science and Medical Technology sector.

Antibiotic Resistance Simulation Capture Sheet, Part 1

ANSWER KEY **Do not share with students**

Directions
Highlight and annotate the following reading.
Then answer the questions that follow.

Antibiotic Resistance

Source: *What is Antibiotic Resistance*

Introduction

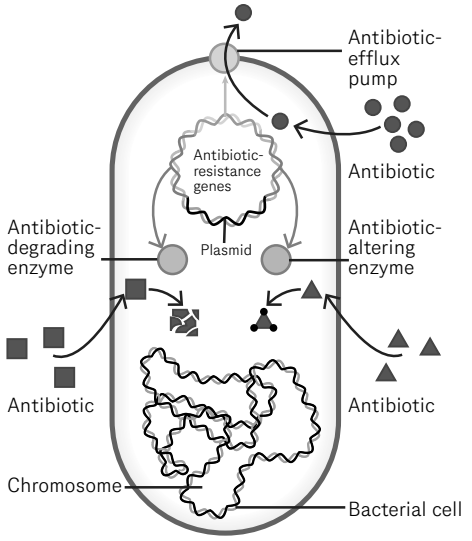
Overuse of antibiotics is creating stronger bacteria. When bacteria become resistant to antibiotics, it can be harder to kill those bacteria and thus harder to treat that bacterial infection. Losing the ability to treat infections is a major threat to public health. Scientists design antibiotics to interact with specific parts of a bacterium's structure or cellular machinery. However, by evolving new traits, bacteria can defeat antibiotics in the following ways:

Natural Selection: The concept of "survival of the fittest" means that the weakest bacteria, or those most susceptible to an antibiotic, will die first. The bacteria that survive have defense mechanisms enabling them to do so, and will pass those traits on to future generations.

Multiple Mutations: Each time DNA is copied, there are errors. The more copies, the more errors. Not all these errors are harmful—some are actually beneficial and could provide genetic changes that lead to defense mechanisms. Because bacteria are extremely numerous, there can be quite a variety in genetic changes and defense mechanisms.

Rapid Reproduction: Bacteria reproduce rapidly, sometimes in as little as 20 minutes. It does not take long for bacteria with antibiotic defense mechanisms—antibiotic-resistant bacteria—to become the majority of a bacterial population.

Methods of Antibiotic Resistance



Antibiotic Resistant Bacteria and Next Steps

The earliest antibiotics were developed in the 1940s. They helped turn the course on diseases such as pneumonia and tuberculosis. However, all of these antibiotics have lost some effectiveness over time—that is, bacteria have acquired defense mechanisms that provide some protection against these drugs. For some infections, there are very few medications available, especially against superbugs that have evolved multiple defense mechanisms. As the cost of developing new antibiotics is quite high, it is important for us to maintain the usefulness of existing ones. It is essential for antibiotics to be used exactly as recommended by a doctor. For example, ending treatment early or taking antibiotics for illnesses not caused by bacteria could lead to antibiotic resistance.

Annotations

Answers will vary.

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Antibiotic Resistance Simulation Capture Sheet, Part 1

ANSWER KEY **Do not share with students**

Continued

1. How do antibiotics function?

By targeting specific parts of the bacteria's structure or cellular machinery.

2. Use the model from the previous page to explain at least two mechanisms bacteria could use to become antibiotic resistant.

Bacteria could pump out the antibiotic, activate genes that break down the antibiotic, or activate genes that modify the antibiotic.

3. Why can a bacterial population gain antibiotic resistance so quickly?

Bacteria reproduce in as little as 20 minutes and have random mutations.

4. Why should we use antibiotics appropriately and only when needed?

They are expensive and overuse can cause side effects, such as leading to antibiotic resistance.

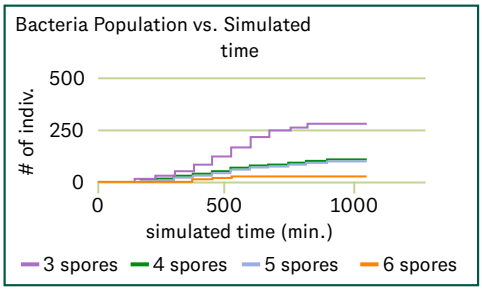
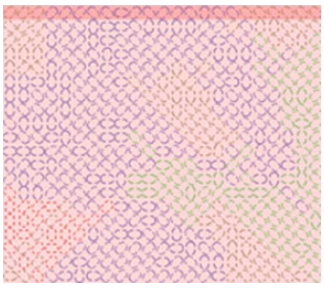
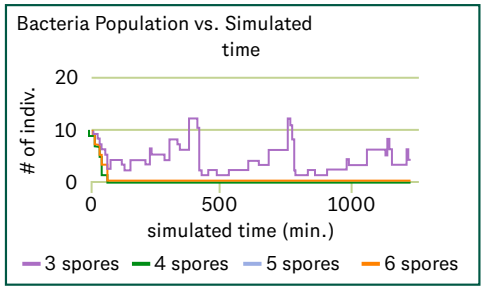
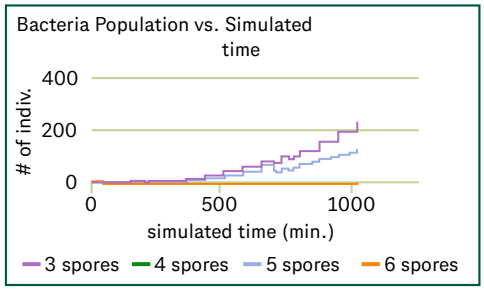
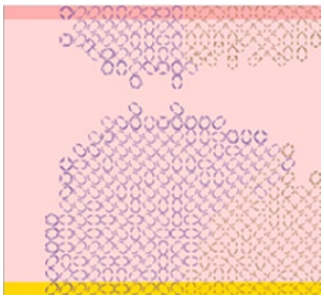
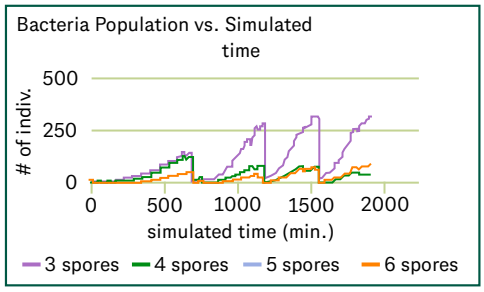
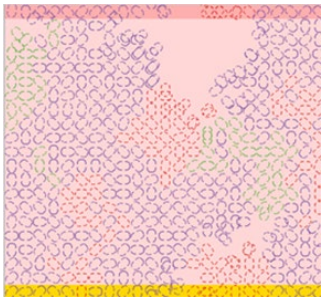
Antibiotic Resistance Simulation Capture Sheet, Part 2

ANSWER KEY — **Do not share with students**

Directions

Fill in the table below with your screenshots or drawings of the population graph and bacteria growth model.

Antibiotic Transfer Table

	Variables	Population Growth Curve	Bacteria Growth Model
A	Half Dose		
B	Normal Dose		
C	Skip Dose 2		
D	Infecting New Patients		

Antibiotic Resistance Simulation Capture Sheet, Part 3

ANSWER KEY **Do not share with students**

Directions
Use the information in your data table to answer the following questions.

1. Observe your population growth curves and bacterial growth models.
    a. Which bacteria were the most successful at surviving? Which were the least successful? What were the differences between these bacteria?

The most successful were the bacteria with 3 pores. The least successful were the bacteria with 6 pores. The difference between these are the amount of pores.

    b. How might these differences be helpful or harmful to bacteria?

More pores make it easier for antibiotics to enter the bacteria, whereas fewer pores make it less likely for the antibiotics to enter.

2. After a dose, the antibiotics that do not hit bacteria and reach the bottom reappear at the top of the simulation. What do you think this represents? How does this mirror real life?

This illustrates how antibiotics remain in the bloodstream between doses and circulate until they are able to kill bacteria.

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Antibiotic Resistance Simulation Capture Sheet, Part 3

ANSWER KEY **Do not share with students**

Continued

3. Based on data from your simulation, why is it important that pharmaceutical companies make pills with a specific amount of medication or antibiotics?

They need to make pills with a high enough dosage to destroy the bacteria. If the dosage is not enough, the bacteria can multiply quickly.

4. Explain similarities and differences in the bacterial growth curves of the original patient and additional patients (second infection, third infection, and fourth infection).

Bacterial populations were composed of different types of bacteria—primarily 3-pore bacteria—and growth curves were much steeper in additional patients, indicating a faster rate of growth and resistance to the antibiotics.

Continues next page >

Antibiotic Resistance Simulation Capture Sheet, Part 3

ANSWER KEY **Do not share with students**

Continued

5. Make a Claim, supported by Evidence and Reasoning to the following question.

Provided are three example CERs. Students provide only one.

Question	Claim (one to two sentence answer to the question)
Given that doctors generally prescribe antibiotics to be taken 2–3 times a day for 7–14 days, not just until the patient feels better, why should patients take their prescription exactly as prescribed?	Bacteria can become resistant to antibiotics through the process of natural selection. (Answers may vary.)

	Evidence (data from the simulation or facts from articles)	Reasoning (an explanation of how your evidence supports your claim)
1	In the graph of the procedure where a patient took a half dose, all four bacterial populations showed steady growth and no sign of eradication.	This procedure had a patient take half of a normal dose, and the result was bacteria continuing to grow within them steadily. The amount of antibiotics they took was not enough to eradicate or slow the growth of any of the bacteria. This is a clear indicator that taking too little antibiotic is detrimental to the patient's health because it is ineffective.
2	In the graph of the procedure where a patient took a normal dose without skipping doses, all four bacterial populations survived and grew steadily, though less than for the patient who took only a half dose.	This procedure had a patient take a normal dose amount without skipping any doses throughout the day. It is clear to see that the growth is slower here than in the previous graph, however none of the bacteria were eradicated, and the ones with the highest growth rates are likely becoming resistant to the antibiotic. This is an indicator that the patient is loading their body with too much antibiotic because they are taking it too often.
3	In the graph of the procedure where a patient took a normal dose but skipped the second dose, the bacterial populations grew at about the same rate as the normal dose without skipping. However, only two bacteria survived and the other two were eradicated.	This procedure had a patient take a normal dose but skip one of their four daily doses. The result of this was two bacteria populations being killed off while the remaining two populations' growth was slowed. This is the best possible outcome out of all three procedures, where we see clear eradication of certain populations and slowed growth of the remaining ones. This indicates that there needs to be a "sweet spot" in the amount of antibiotic prescribed; too much or too little (or too often or not often enough) can both be detrimental to the patient.

When a Virus is the Cure Capture Sheet

ANSWER KEY **Do not share with students**

Directions
As you read the article, answer questions in the right hand column to help process your understanding of phage therapy.

When a Virus is the Cure *(Abbreviated)*	Source: The New Yorker by Nicola Twilley, December 14, 2020

Before reading the article, why do you think phage therapy is not our go-to therapy to treat bacterial infections?

Phage therapy is a newer treatment and may still require approval for use.

Some years before Joseph Bunevacz came to America, and decades before he gota sick, he taught the Beatles how to ski. Or so he told me when I visited him at his home, on the arid northeastern slopes of the mountains that separate Los Angeles from the Mojave Desert, to learn more about an experimental medical treatment that he was hoping to receive for a strange and persistent infection in his blood. His wife, Filomena, took me through his medical history, consulting a stack of yellow legal pads in which, for the past five years, she has recorded countless tests and treatments. Yet Bunevacz, a bright-eyed seventy-nine-year-old with a shock of white hair, wearing an official Hungarian Olympic tracksuit, just wanted to tell wild, improbable stories about his younger years.

Whenever Bunevacz paused for breath, Filomena, a retired nurse, filled me in on the dates of his various scans, his handful of colonoscopies, his gall-bladder operation, his bile-duct stent, the surgical removal of his upper colon, and his trips to urgent care. “Do you know how many blood cultures they have done on this man?” she said. “When I was a nurse, the patients who were this sick—they died.”

Despite his irrepressible good humor, Bunevacz is, indeed, very unwell. His case is also something of a medical mystery. His symptoms—fever, nausea, abdominal pain, and diarrhea—are easily explained: he is being poisoned by *E. coli* bacteria in his bloodstream. But it is not clear what has been causing the infection to recur. When I saw him, Bunevacz had been going to his local emergency clinic every month, in order to receive huge doses of antibiotics, but after each treatment ended the infection would return. For years, doctors from across the country have scanned him, probed him, and sliced him open to inspect or remove the tissue in which they suspect the *E. coli* may lurk. Nothing has made the slightest difference.

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When a Virus is the Cure Capture Sheet

ANSWER KEY **Do not share with students**

Continued

"Honestly, I would have thought he would have died from this a year ago," Emily Blodget, his infectious-disease consultant at the University of Southern California's Keck Hospital, told me.

Late last year, the Bunevaczes' daughter came up with a new suggestion: an emergency treatment, not yet approved by the F.D.A., that had saved the life of a man in San Diego. "She called and said, 'Mom, you have to get Dad to do phage therapy,'" Filomena told me. "P-H-A-G-E," Bunevacz clarified, nodding. So Filomena asked Blodget whether he might be a candidate for this mysterious new medicine.

Why are the antibiotics not able to kill the *E. coli* in his system?

1. They have phages.
2. They have become resistant to antibiotics.
3. They have CRISPR-Cas9 to fight against antibiotics.

Phages, or bacteriophages, are viruses that infect only bacteria. Each kingdom of life—plants, animals, bacteria, and so on—has its own distinct complement of viruses. Animal and plant viruses have always received most of our scientific attention because they pose a direct threat to our health, and that of our livestock and crops. The well-being of bacteria has, understandably, been of less concern, yet the battle between viruses and bacteria is brutal: scientists estimate that phages cause a trillion trillion infections per second, destroying half the world's bacteria every forty-eight hours. As we are now all too aware, animal-specific viruses can mutate enough to infect a different animal species. But they will not attack bacteria, and bacteriophage viruses are similarly harmless to animals, humans included. Phage therapy operates on the principle that the enemy of our enemy could be our friend.

If Bunevacz's doctors could find a virus that infected his particular strain of *E. coli*, it might succeed where antibiotics had failed.

"The enemy of our enemy is my friend." You may have heard this phrase used elsewhere. What danger might there be in thinking this way?

Caution needs to be taken when developing new therapies that may have unintended consequences.

Can phages directly harm humans and infect our own cells?

1. Yes, if they are given the right conditions.
2. No, they are specific to bacteria.

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When a Virus is the Cure Capture Sheet

ANSWER KEY **Do not share with students**

Continued

Last year, a paper published in Nature Medicine documented the role of phages in saving the life of a teenage cystic-fibrosis patient in the U.K. who was stricken with a bacterial infection after a double-lung transplant. Another case study described how phages helped save a Minnesota man's leg, which had become infected after knee surgery.

In the past five years, phage research has accelerated, with a proliferation of articles in publications, conferences, and pharmaceutical-company investment. This enthusiasm reflects the ever-growing threat of antibiotic-resistant bacteria and a dearth of new antibiotics available to fight them. In 2016, the United Nations pronounced antibiotic resistance "the greatest and most urgent global risk." Without reliable antibiotics, even relatively routine surgery—Cesarean sections, hernia repair, appendix or tonsil removal—could be deadly. One analysis published in a leading British medical journal estimated that, without antibiotics, one in seven people undergoing routine hip-replacement surgery might die from a drug-resistant infection. Already, some seven hundred thousand people die each year as a direct result of drug-resistant infections, a number that is predicted to rise to ten million by 2050.

Soon after Thanksgiving last year, he was identified as a viable candidate for the therapy, and Blodget told him that she thought it was worth a try. "I said, I don't think it's going to hurt, and it can possibly help," she recalled. "I mean, at this point, there's nothing else to do."

The explanation for Blodget's initial hesitance can be found in phage therapy's complicated history. Although it is still considered an experimental treatment in the United States, phages have been used to treat and prevent bacterial infections since their discovery, more than a century ago. For many American doctors, the obvious next question is: If they actually work, wouldn't we know by now?

Part of the problem with phages is that they were discovered almost too early—far in advance of the technology and scientific understanding required to use them effectively. French-Canadian scientist, Félix d'Hérelle, was an autodidact working as a volunteer at the Institut Pasteur, in Paris.

After "proving" the safety of phages by feeding them to himself, his young family, and some of his colleagues, d'Hérelle went on to inject them into the swollen lymph nodes of four people who had bubonic plague, effecting a seemingly miraculous cure. Phages were briefly all the rage: in 1925, Sinclair Lewis used them to tackle a fictional outbreak in his Pulitzer Prize-winning novel, "Arrowsmith."

At this time, no one had seen a phage. An *E. coli* bacterium, two-thousandths of a millimetre long, is almost as small as the shortest wavelengths of light visible to the human eye under magnification, whereas the phages that attack it are a tenth of that size, or a hundred times smaller than the smallest thing we can see. Only with the invention of the transmission electron microscope, in the 1930s, did phages become visible, but because the first images were published in Nazi Germany, it was years before British and American scientists saw them. Even today, most scientists "see" a phage only by the destruction it has wreaked on bacteria in a Petri dish—clear, glassy zones of death scattered across a soupy, yellowish microbial lawn.

In the 1930s, d'Hérelle, who was sympathetic to Communist ideals, was invited by Stalin to help establish a center for phage-therapy research in Tbilisi, which was in the Soviet republic of Georgia. During the Second World War, Soviet and German military medics carried vials of phages as part of their field kits to prevent infection of wounds and burns. That connection with America's adversaries made phages seem ideologically suspect to many in the West. As the medical historian William Summers has written, phage therapy acquired a "Soviet taint" in the postwar period, becoming "scientifically unsound because it was politically unsound."

Still, as late as 1961, phage therapy had some American adherents, including Elizabeth Taylor, who received a dose of staph bacteriophage when she developed near-fatal pneumonia during the filming of "Cleopatra" and needed an emergency tracheotomy. By then, however, phage therapy had been superseded by penicillin, which had become widely available in the West after the war and quickly established itself as the preferred treatment for bacterial infections. Doctors in Eastern Europe continued to prescribe phages—delivered both topically and orally in powders, sprays, and syrups—but their counterparts on the other side of the Iron Curtain had, for the most part, barely even heard of them. Phages were still studied—Francis Crick and James Watson, two of the discoverers of the double-helix structure of DNA, both conducted phage research—but they were not part of modern medicine in Western Europe and the United States.

Give at least two reasons why phage therapy is only now getting attention in the United States

— It was discovered by Germany during WWII but because of political tensions, the United States was skeptical of it.

— Afterward, antibiotics seemed to be the ideal treatment of bacterial infections until now, when antibiotic resistance has become apparent.

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When a Virus is the Cure Capture Sheet

ANSWER KEY **Do not share with students**

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The rise of antibiotic-resistant bacteria was predicted by Alexander Fleming, the Scottish bacteriologist who discovered penicillin. In 1945, just seventeen years after his accidental breakthrough, he warned, "There is the danger that the ignorant man may easily underdose himself, and by exposing his microbes to nonlethal quantities of the drug, make them resistant." As early as 1947, penicillin-resistant staphylococcus bacteria were found in hospitals in England, but few heeded Fleming's warning. Antibiotics were systematically overused and abused (including as a growth aid in factory-farmed livestock), giving rise to a microbiological arms race in which bacteria mutated new forms of resistance and scientists raced to develop powerful new classes of antibiotic. To make matters worse, fears of antibiotic resistance have, in recent decades, created a perverse incentive in medical research: new antibiotics, to remain effective, must be used sparingly, as so-called antibiotics of last resort. As a result, it is almost impossible to recoup the cost of developing them. No significant new antibiotics have been introduced since the 1980s, and, in 2001, the World Health Organization issued an urgent call-to-action to tackle antibiotic resistance. Phages were ready for their renaissance.

In November, 2015, Steffanie Strathdee, an infectious-disease epidemiologist at the U.C. San Diego School of Medicine, went on a vacation to Egypt with her husband, Tom Patterson, a professor of psychiatry. After visiting the pyramids, Patterson, sixty-eight at the time, became violently sick with what they at first assumed was food poisoning. But Egyptian doctors gave him a diagnosis of acute pancreatitis, and he was medevaced to Frankfurt, where tests revealed that he also had an abscess infected with a deadly, drug resistant strain of *Acinetobacter baumannii*. Doctors tested his infection against fifteen powerful antibiotics, but only three had even a slight effect. Another air ambulance brought Patterson home to San Diego, where, within weeks, his infection evolved immunity to those three antibiotics, too. Patterson's organs had begun to fail—first his heart and his lungs, and soon, it seemed, his kidneys—and he went into a coma. By the third week of February, 2016, his doctor, Robert Schooley, warned Strathdee that they were out of options.

Searching the biomedical literature for alternative treatments, Strathdee found a reference to phage therapy. She and Schooley, a human virologist by training, started contacting phage researchers around the world to see if any of them had a virus that might kill Patterson's bug. They received phages originally isolated from sewage plants, Texas dirt, and lagoons of swine and cattle manure; colleagues then grew them in bulk and purified the resulting solution. Schooley received special approval from the FDA to inject some phages into the plastic tubing draining fluid from Patterson's abdominal cavity, near where the infection had originated, and to pump others directly into a vein. Three days later, Patterson emerged from his coma; after a few months, he was discharged, his infection entirely eradicated.

As Patterson underwent months of physical therapy and rehabilitation, Strathdee and Schooley began publicizing his case, describing it in a scientific paper, giving talks, and providing expert testimony to the National Institutes of Health. In July, 2018, they founded the first phage-therapy center in North America, the Center for Innovative Phage Applications and Therapeutics (IPATH), at U.C. San Diego, and began to build a library of phages. Patterson and Strathdee published a joint memoir about his miraculous recovery, and, as word started to spread, emails, calls, and Facebook messages began to flood in from people desperately hoping that phages could help their loved ones too. It was Patterson's case that Joseph Bunevacz's daughter had heard about, and late last year Strathdee promised to take me along on her next phage-trapping expedition as part of a national search to identify a phage that could kill Bunevacz's pernicious *E. coli*.

Finding phages is not in itself particularly challenging: The average teaspoon of seawater holds five times more phages than there are people in Rio de Janeiro; for every grain of sand in the world, there are a trillion phages. But the best place to find phages that will kill drug-resistant bacteria is where people or animals have shed them—in other words, sewage.

Why are sewage treatment plants and lagoons of swine and cattle good places to search for phages?

The best place to find phages that will kill drug-resistant bacteria is where people or animals have shed them—in other words, sewage.

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When a Virus is the Cure Capture Sheet

ANSWER KEY **Do not share with students**

Continued

The timing of a successful phage hunt in Southern California is thus strongly correlated with rainfall. I drove to Carlsbad, just north of San Diego, to meet Strathdee and Patterson for a day of phage hunting.

We filled vials with dubious brown liquid from the end of a rusted pipe, from water that had a coyote turd floating in it, and from the rotting, shrimp-scented swampy edges of the slough. We labeled each sample with a date and a number, and dropped them in ziplock bags in the cooler. Then she and Patterson drove home, and I took our spoils to U.C. San Diego to meet Hedieh Attai, a postdoctoral researcher.

Attai keeps a freezer of *E. coli*, *Enterococcus*, and *Pseudomonas*—three of the six pathogens that together cause most hospital-acquired infections. Wearing a lab coat, goggles, and gloves, she put a dish of nutrient-rich jelly on a turntable and then, in a process that resembled coating a frying pan with oil, swirled it to distribute a layer of pathogenic *E. coli*. Elsewhere, our samples were sucked through a filter with pores small enough to remove any bacteria, leaving only the phages. The previously murky liquid came out crystal clear—it looked good enough to drink. "I can't let you do that," Attai said, with a nervous laugh. She did, however, let me draw the phage samples into a syringe and squirt a series of identical droplets onto the bacterial film.

If none of the phages we'd found were capable of attacking these particular bacteria, the pathogenic microbes would continue growing undisturbed. But, if the liquid contained a single phage that was a match for this particular host, that phage would bind to the bacterial cell membrane and insert its genome into the fluid-filled interior. Once inside an *E. coli* cell, the phage would take over, mimicking and exploiting the bacterium's own signaling pathways in order to force the cell's protein-manufacturing machinery to start printing out copy after copy of the phage genome instead. Eventually, the *E. coli* cell would become so stuffed with phage copies that it would burst, releasing a horde of phages ready to invade the next bacterial cell. We would know in a day or two if our phage had been successful by the appearance of a circle of dead microbes puncturing the thick layer of *E. coli*.

How is this similar to using antibiotics?

1. They both attack the cell wall or cell machinery of the bacterium.
2. They are both chemicals.
3. They can both kill viruses effectively.

Schooley's major challenge has been securing a phage supply. "We could have started it two and a half years ago if we had a phage source," he said. The pandemic has delayed the trial yet further. In the meantime, a handful of labs and small startups volunteer their time and their phage libraries to help treat sick patients; finding an institution or a company that is willing and able to invest in the basic clinical trials needed to learn how phages work has been all but impossible.

Forest Rohwer, a microbial ecologist at San Diego State University, pointed to a more fundamental problem. In a dynamic ecosystem, whether a coral reef or our bodies, enemies and friends are situational rather than static. Indeed, phage viruses are responsible for creating the majority of pathogenic bacteria in the first place, thanks to their ability to move genes around. An *E. coli* bacterium is usually harmless until it acquires virulence genes from an invading temperate phage. A cholera outbreak is both triggered by phages and halted by them: one kind of phage donates a virulence gene to cholera bacteria, causing it to expand its range, only for another kind to hijack those newly vulnerable pathogenic bacteria to make copies of itself. Sick or healthy humans are just a side effect. Although Rohwer is excited about phage's therapeutic possibilities—his lab purified part of Tom Patterson's phage cocktail—he worries that our ambitions to manipulate an entire ecosystem within the human body might overstep our abilities, and that the unintended consequences might be as unwelcome as the pathogenic bacteria itself. "They can kill you, no problem," he said. "You get the wrong phage and the right bacteria and you're dead."

How is phage therapy potentially dangerous?

1. The phages can get into human cells.
2. The phages cause mutations in the bacteria they infect.
3. The phages can get into the water supply and infect other humans.

Phage therapy thus continues to be a boutique affair—just a few patients, each treated with a personalized phage cocktail scavenged from moldy eggplants, cesspools, and pig farms. It's also hit-and-miss: the phages that Strathdee and I collected at Batiquitos Lagoon turned out, unfortunately, not to be a good match for Joseph Bunevacz's infection. There was better news from Baylor College of Medicine where researchers had isolated phages that were active against Joseph Bunevacz's *E. coli* infection. As Southern California emerged from late-spring rains into a dazzling superbloom, Filomena texted me a photo of the couple embracing on a hillside blanketed with poppies. As it turned out, the coronavirus outbreak was about to slow everything down, and it was late fall before his treatment received FDA approval. This month, Bunevacz should finally be able to start his phage therapy. "It's a beautiful life," he said when I met him. "And I'd like to push it a little longer."

Clinical Trials for a New Phage Therapy, Part 2

ANSWER KEY **Do not share with students**

Directions

In groups, follow the steps below to take the role of Tom's wife, Steffanie, in deciding if she should enter him into the PHAG-O-HEAL clinical trail.

1. Read and reflect on the background information below.

   Clinical trials for phage therapy have been limited to a few people and cases so far. One reason for this is because antibiotics are more easily available and are safer to use. Remember, phages are 'alive' and can mutate, or change, over time, which would affect the bacteria they are targeting. Per the FDA, the risk is not worth the reward, but that may change with the looming antibiotic crisis. According to the *CDC*, more than 2.8 million antibiotic-resistant infections occur in the United States each year, and more than 35,000 people die as a result. The national cost of these infections is more than $4.6 billion annually.

2. Recall the *How Sewage Saved My Husband's Life from a Superbug video* from Day 1 that was paused at 06:00. Dr. Steffanie Strathdee, Tom's wife, finds a clinical trial called PHAG-O-HEAL that might work for Tom.

3. Read the *Phage Therapy Clinical Trial Overview* and help Steffanie understand all the information about this clinical trial to determine if Tom should be included. Note that *E. coli* and *P. aeruginosa* are two bacteria that can be resistant to antibiotics.

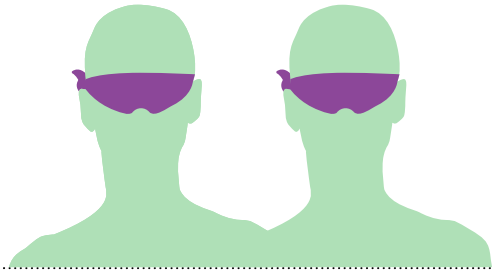
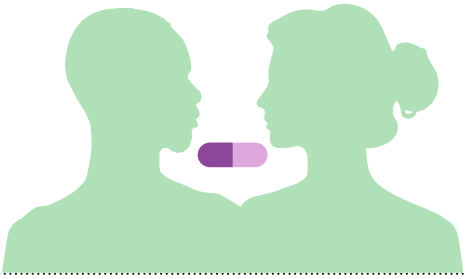
Continues next page >

Clinical Trials for a New Phage Therapy, Part 2

ANSWER KEY **Do not share with students**

Continued

4. Write a definition (in your own words) and include a picture for following vocabulary terms using a *Glossary* from *ClinicalTrials.gov*.

	Word	Definition	Picture
1	Double-blind	Denoting a test or trial, especially of a drug, in which any information that may influence the behavior of the tester or the subject is withheld until after the test.	
2	Randomized	Of an experiment or procedure performed using random selection or sampling.	
3	Open-label	A type of clinical trial in which information is not withheld from trial participants; In particular, both the researchers and participants know which treatment is being administered.	
4	Multicentric	A clinical trial conducted at more than one medical center or clinic.	

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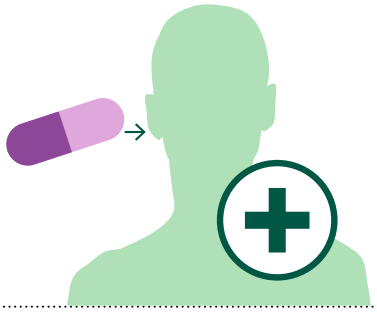
Clinical Trials for a New Phage Therapy, Part 2

ANSWER KEY **Do not share with students**

Continued

	Word	Definition	Picture
5	Efficacy	The ability to produce a desired or intended result.	
6	Inclusion Criteria	These are the reasons that a person is allowed to participate in a clinical study.	
7	Exclusion Criteria	These are the reasons that a person is not allowed to participate in a clinical study.	

Clinical Trials for a New Phage Therapy, Part 3

ANSWER KEY — **Do not share with students**

Directions
Select three of the following questions and use the information from the reading to answer them.

1	What is being studied?
2	What possible interventions might I receive during the trial?
3	Who will know which intervention I receive? Will I know? Will the research team?
4	What will I have to do?
5	What tests and procedures are involved?
6	Will hospitalization be required?
7	How long will the study last?
8	What type of long-term follow-up care is part of this trial?

Note to teacher: Answers to all questions provided below.
Students should only select three questions to answer.

#	Your Answer
1	Local bacteriophage treatment of antibiotic-resistant bacterial infections, such as *E. coli* or *P. aeruginosa* septic (whole body) infections, in patients is being studied.
2	The possible interventions that you might receive during the trial are *E. coli* phages cocktails, standard of care antibiotic cocktails, and *P. aeruginosa* phages cocktails.
3	Both the members of the research team and you will know which intervention you receive during the trial since this is an open-label clinical trial. Information will not be withheld from you.
4	You will have to receive local bacteriophage treatments of septic infections due to *E. Coli* or *P. aeruginosa* using Pharma anti-*E. coli* and anti-*P. aeruginosa* bacteriophage cocktails.
5	Members of the research team will have to measure the time for bacteria reduction adjusted on the antibiotic treatment you receive, assess the tolerance of the treatment, and measure the incidence and delay of infection reduction. The procedures will be randomized, or performed using random selection or sampling.
6	It appears you will have to stay at the hospital or clinic until the study is over.
7	The study will last 35 days or five weeks.
8	I don't see evidence that there is long-term follow-up care as part of this trial.

Clinical Trials for a New Phage Therapy, Part 4

ANSWER KEY — **Do not share with students**

Directions

Use the following information to help Steffanie determine if she should enroll her husband in the trial.

1. For each indicator, consider why it is important to ensure these criteria are met.

   Source: *Study Management—Clinical Trial Resources— Clinical Trials Resource Center*

	Indicator(s)	Criteria	Why is it important to ask this question?
A	Informed Consent and Documentation	Is it documented that the study has been explained and signed by the participant and/or legally authorized representative allowing for the opportunity to ask questions?	It is important to properly explain the risks of a clinical trial, especially since even though precautions are taken there are still potential dangers in participating. It is important that the participant or legally authorized representative understand these risks.
B	Eligibility Criteria	Has the participant met all Inclusion Criteria and Exclusion Criteria for the study?	The inclusion and exclusion criteria are important to make sure the patient is able to safely participate in the study and benefit from the study.
C	Prohibited/Concomitant Medications	Is the participant taking any prohibited medications? If yes, was this finding documented and the PI notified?	It is important to make sure any medications that may conflict with the treatment are accounted for.

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Clinical Trials for a New Phage Therapy, Part 4

ANSWER KEY **Do not share with students**

Continued

2. Should Tom participate in this clinical trial? Explain your reasoning.

Student answers will vary, there should be no incorrect choice as long as students explain their reasoning.

3. Tom, of course, is not the only person who may or may not participate in this trial. Check out some of the ideas listed in *The Complete Guide to Remarkable Patient Engagement With Clinical Trials* from MDGroup. How can a more diverse patient group be engaged and recruited in this clinical trial? Choose one idea to expand on.

Student answers will vary, there should be no incorrect choice as long as students explain their reasoning.

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Antibiotic Resistance Simulation Capture Sheet, Part 1

Directions
Highlight and annotate the following reading.
Then answer the questions that follow.

Antibiotic Resistance

Source: *What is Antibiotic Resistance*

Introduction

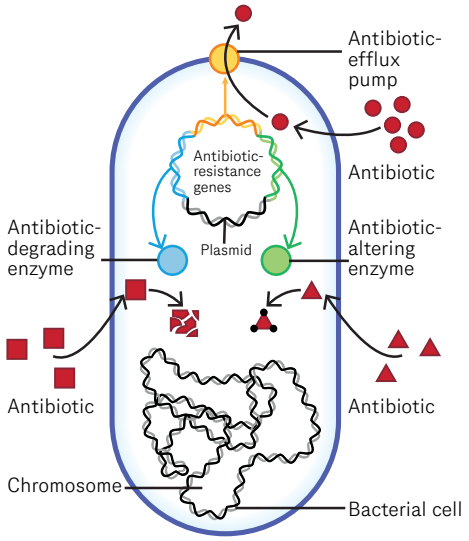
Overuse of antibiotics is creating stronger bacteria. When bacteria become resistant to antibiotics, it can be harder to kill those bacteria and thus harder to treat that bacterial infection. Losing the ability to treat infections is a major threat to public health. Scientists design antibiotics to interact with specific parts of a bacterium's structure or cellular machinery. However, by evolving new traits, bacteria can defeat antibiotics in the following ways:

Natural Selection: The concept of "survival of the fittest" means that the weakest bacteria, or those most susceptible to an antibiotic, will die first. The bacteria that survive have defense mechanisms enabling them to do so, and will pass those traits on to future generations.

Multiple Mutations: Each time DNA is copied, there are errors. The more copies, the more errors. Not all these errors are harmful—some are actually beneficial and could provide genetic changes that lead to defense mechanisms. Because bacteria are extremely numerous, there can be quite a variety in genetic changes and defense mechanisms.

Rapid Reproduction: Bacteria reproduce rapidly, sometimes in as little as 20 minutes. It does not take long for bacteria with antibiotic defense mechanisms—antibiotic-resistant bacteria—to become the majority of a bacterial population.

Methods of Antibiotic Resistance



Antibiotic Resistant Bacteria and Next Steps

The earliest antibiotics were developed in the 1940s. They helped turn the course on diseases such as pneumonia and tuberculosis. However, all of these antibiotics have lost some effectiveness over time—that is, bacteria have acquired defense mechanisms that provide some protection against these drugs. For some infections, there are very few medications available, especially against superbugs that have evolved multiple defense mechanisms. As the cost of developing new antibiotics is quite high, it is important for us to maintain the usefulness of existing ones. It is essential for antibiotics to be used exactly as recommended by a doctor. For example, ending treatment early or taking antibiotics for illnesses not caused by bacteria could lead to antibiotic resistance.

Annotations

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Antibiotic Resistance Simulation Capture Sheet, Part 1

Continued

1. How do antibiotics function?

2. Use the model from the previous page to explain at least two mechanisms bacteria could use to become antibiotic resistant.

3. Why can a bacterial population gain antibiotic resistance so quickly?

4. Why should we use antibiotics appropriately and only when needed?

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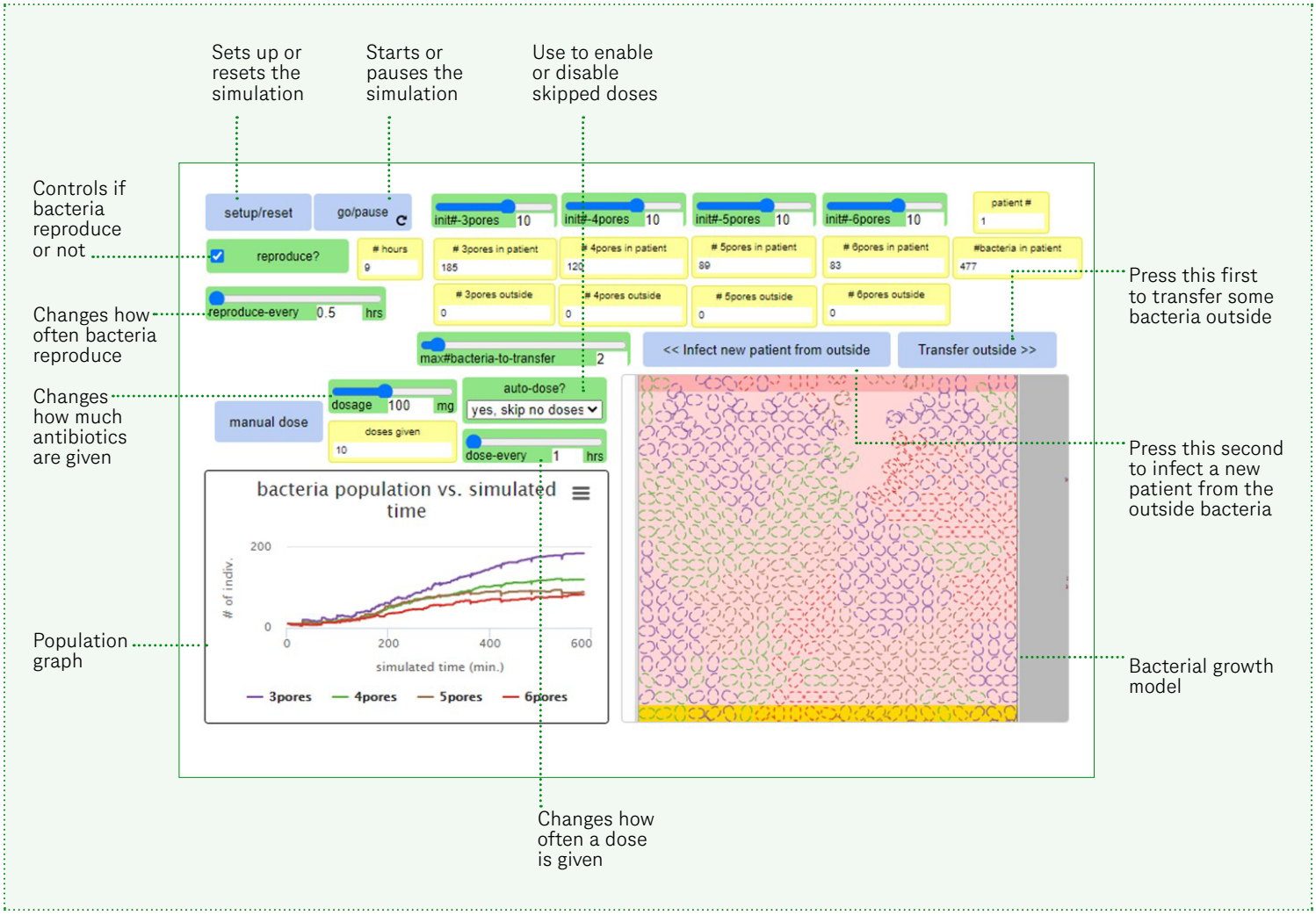
Antibiotic Resistance Simulation Instructions

Directions

Visit Bacteria Infection Antibiotics Transfer: NetLogo Web. Follow the procedure to simulate the effect of antibiotics on bacterial growth. Record observations in the Antibiotic Transfer Table in the Antibiotic Resistance Simulation Capture Sheet, Part 2.

1. Review this diagram of the website before beginning the procedure outlined on the next page.



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Antibiotic Resistance Simulation Instructions

Continued

2. Follow the three procedures as outlined below (A, B and C). Check with your teacher before continuing on to follow procedure D.

A		Half Dose at 1,000 Ticks
☐	1	Set the following parameters: a. Check the "reproduce" box. b. Set "reproduce-every" to 1.25 hours. c. Change the "dosage" to 100 mg. d. Make sure "auto dose" is set to yes, skip no doses. e. Set "dose-every" to 6 hours.
☐	2	Press the setup/reset, then press go/pause. *If all bacteria die in the initial wave, you may want to reset the simulation and try again so they survive more than the first wave.*
☐	3	Observe the simulation for 1,000 minutes/ticks. Press pause when you get to 1,000 ticks.
☐	4	Take a screenshot or draw a picture of the population graph and bacteria growth model. Insert in the "Half Dose" row in the Antibiotic Transfer Table.

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Antibiotic Resistance Simulation Instructions

Continued

B		Normal Dose at 1,000 Ticks
☐	1	Change the parameters to the following: *the only difference is the dosage amount.* a. Check the "reproduce" box. b. Set "reproduce-every" to 1.25 hours. c. *Change the "dosage" to 200 mg.* d. Make sure "auto dose" is set to yes, skip no doses. e. Set "dose-every" to 6 hours.
☐	2	Press the setup/reset, then press go/pause. *If all bacteria die in the initial wave, you may want to reset the simulation and try again so they survive more than the first wave.*
☐	3	Observe the simulation for 1,000 minutes/ticks. Press pause when you get to 1,000 ticks.
☐	4	Take a screenshot or draw a picture of the population graph and bacteria growth model. Insert in the "Normal Dose" row in the Antibiotic Transfer Table.
C		Skip Dose 2 at 1,000 Ticks
☐	1	Change the parameters to the following: *same original dosage, change autodose to yes, skip dose 2.* a. Check the "reproduce" box. b. Set "reproduce-every" to 1.25 hours. c. Change the "dosage" to 200 mg. d. *Make sure "auto dose" is set to yes, skip dose 2.* e. Set "dose-every" to 6 hours.
☐	*	Follow steps two through four (2–4) as outlined above.

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Antibiotic Resistance Simulation Instructions

Continued

Check with your teacher before beginning step D of the procedure.

D		Infecting New Patients
☐	1	Change the parameters to the following: a. Check the “reproduce” box. b. Set “reproduce-every” to 1.25 hours. c. Change the “dosage” to 200 mg. d. Make sure “auto dose” is set to yes, skip dose 2. e. Set “dose-every” to 6 hours. f. Set “max # bacteria to transfer” to 40.
☐	2	After approximately 500 ticks, click “Transfer outside” and then “infect new patient from outside.”
☐	3	Allow 500 more ticks then repeat step 2, infecting a third patient.
☐	4	Allow 500 more ticks then repeat step 2, infecting a fourth patient.
☐	5	Take a screenshot or draw a picture of the population graph and bacteria growth model. Insert in the “Normal Dose” row in the Antibiotic Transfer Table.

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Antibiotic Resistance Simulation Capture Sheet, Part 2

Directions
Fill in the table below with your screenshots or drawings of the population graph and bacteria growth model.

Antibiotic Transfer Table

	Variables	Population Growth Curve	Bacteria Growth Model
A	Half Dose		
B	Normal Dose		
C	Skip Dose 2		
D	Infecting New Patients		

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Antibiotic Resistance Simulation Capture Sheet, Part 3

Directions
Use the information in your data table to answer the following questions.

1. Observe your population growth curves and bacterial growth models.
   a. Which bacteria were the most successful at surviving? Which were the least successful? What were the differences between these bacteria?
   b. How might these differences be helpful or harmful to bacteria?

2. After a dose, the antibiotics that do not hit bacteria and reach the bottom reappear at the top of the simulation. What do you think this represents? How does this mirror real life?

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Antibiotic Resistance Simulation Capture Sheet, Part 3

Continued

3. Based on data from your simulation, why is it important that pharmaceutical companies make pills with a specific amount of medication or antibiotics?

4. Explain similarities and differences in the bacterial growth curves of the original patient and additional patients (second infection, third infection, and fourth infection).

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Antibiotic Resistance Simulation Capture Sheet, Part 3

Continued

5. Make a Claim, supported by Evidence and Reasoning to the following question.

Question	Claim (one to two sentence answer to the question)
Given that doctors generally prescribe antibiotics to be taken 2–3 times a day for 7–14 days, not just until the patient feels better, why should patients take their prescription exactly as prescribed?	

Evidence (data from the simulation or facts from articles)	Reasoning (an explanation of how your evidence supports your claim)

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When a Virus is the Cure Capture Sheet

Directions

As you read the article, answer questions in the right hand column to help process your understanding of phage therapy.

When a Virus is the Cure

(Abbreviated)

Source: The New Yorker
by Nicola Twilley,
December 14, 2020

Before reading the article, why do you think phage therapy is not our go-to therapy to treat bacterial infections?

Some years before Joseph Bunevacz came to America, and decades before he got sick, he taught the Beatles how to ski. Or so he told me when I visited him at his home, on the arid northeastern slopes of the mountains that separate Los Angeles from the Mojave Desert, to learn more about an experimental medical treatment that he was hoping to receive for a strange and persistent infection in his blood. His wife, Filomena, took me through his medical history, consulting a stack of yellow legal pads in which, for the past five years, she has recorded countless tests and treatments. Yet Bunevacz, a bright-eyed seventy-nine-year-old with a shock of white hair, wearing an official Hungarian Olympic tracksuit, just wanted to tell wild, improbable stories about his younger years.

Whenever Bunevacz paused for breath, Filomena, a retired nurse, filled me in on the dates of his various scans, his handful of colonoscopies, his gall-bladder operation, his bile-duct stent, the surgical removal of his upper colon, and his trips to urgent care. “Do you know how many blood cultures they have done on this man?” she said. “When I was a nurse, the patients who were this sick—they died.”

Despite his irrepressible good humor, Bunevacz is, indeed, very unwell. His case is also something of a medical mystery. His symptoms—fever, nausea, abdominal pain, and diarrhea—are easily explained: he is being poisoned by *E. coli* bacteria in his bloodstream. But it is not clear what has been causing the infection to recur. When I saw him, Bunevacz had been going to his local emergency clinic every month, in order to receive huge doses of antibiotics, but after each treatment ended the infection would return. For years, doctors from across the country have scanned him, probed him, and sliced him open to inspect or remove the tissue in which they suspect the *E. coli* may lurk. Nothing has made the slightest difference.

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When a Virus is the Cure Capture Sheet

Continued

"Honestly, I would have thought he would have died from this a year ago," Emily Blodget, his infectious-disease consultant at the University of Southern California's Keck Hospital, told me.

Late last year, the Bunevaczes' daughter came up with a new suggestion: an emergency treatment, not yet approved by the F.D.A., that had saved the life of a man in San Diego. "She called and said, 'Mom, you have to get Dad to do phage therapy,' " Filomena told me. "P-H-A-G-E," Bunevacz clarified, nodding. So Filomena asked Blodget whether he might be a candidate for this mysterious new medicine.

Why are the antibiotics not able to kill the *E. coli* in his system?

1. They have phages.
2. They have become resistant to antibiotics.
3. They have CRISPR-Cas9 to fight against antibiotics.

Phages, or bacteriophages, are viruses that infect only bacteria. Each kingdom of life—plants, animals, bacteria, and so on—has its own distinct complement of viruses. Animal and plant viruses have always received most of our scientific attention because they pose a direct threat to our health, and that of our livestock and crops. The well-being of bacteria has, understandably, been of less concern, yet the battle between viruses and bacteria is brutal: scientists estimate that phages cause a trillion infections per second, destroying half the world's bacteria every forty-eight hours. As we are now all too aware, animal-specific viruses can mutate enough to infect a different animal species. But they will not attack bacteria, and bacteriophage viruses are similarly harmless to animals, humans included. Phage therapy operates on the principle that the enemy of our enemy could be our friend.

If Bunevacz's doctors could find a virus that infected his particular strain of *E. coli*, it might succeed where antibiotics had failed.

"The enemy of our enemy is my friend." You may have heard this phrase used elsewhere. What danger might there be in thinking this way?

Can phages directly harm humans and infect our own cells?

1. Yes, if they are given the right conditions.
2. No, they are specific to bacteria..

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When a Virus is the Cure Capture Sheet

Continued

Last year, a paper published in Nature Medicine documented the role of phages in saving the life of a teenage cystic-fibrosis patient in the U.K. who was stricken with a bacterial infection after a double-lung transplant. Another case study described how phages helped save a Minnesota man's leg, which had become infected after knee surgery.

In the past five years, phage research has accelerated, with a proliferation of articles in publications, conferences, and pharmaceutical-company investment. This enthusiasm reflects the ever-growing threat of antibiotic-resistant bacteria and a dearth of new antibiotics available to fight them. In 2016, the United Nations pronounced antibiotic resistance "the greatest and most urgent global risk." Without reliable antibiotics, even relatively routine surgery—Cesarean sections, hernia repair, appendix or tonsil removal—could be deadly. One analysis published in a leading British medical journal estimated that, without antibiotics, one in seven people undergoing routine hip-replacement surgery might die from a drug-resistant infection. Already, some seven hundred thousand people die each year as a direct result of drug-resistant infections, a number that is predicted to rise to ten million by 2050.

Soon after Thanksgiving last year, he was identified as a viable candidate for the therapy, and Blodget told him that she thought it was worth a try. "I said, I don't think it's going to hurt, and it can possibly help," she recalled. "I mean, at this point, there's nothing else to do."

The explanation for Blodget's initial hesitance can be found in phage therapy's complicated history. Although it is still considered an experimental treatment in the United States, phages have been used to treat and prevent bacterial infections since their discovery, more than a century ago. For many American doctors, the obvious next question is: If they actually work, wouldn't we know by now?

Part of the problem with phages is that they were discovered almost too early—far in advance of the technology and scientific understanding required to use them effectively. French-Canadian scientist, Félix d'Hérelle, was an autodidact working as a volunteer at the Institut Pasteur, in Paris.

After "proving" the safety of phages by feeding them to himself, his young family, and some of his colleagues, d'Hérelle went on to inject them into the swollen lymph nodes of four people who had bubonic plague, effecting a seemingly miraculous cure. Phages were briefly all the rage: in 1925, Sinclair Lewis used them to tackle a fictional outbreak in his Pulitzer Prize-winning novel, "Arrowsmith."

At this time, no one had seen a phage. An *E. coli* bacterium, two-thousandths of a millimetre long, is almost as small as the shortest wavelengths of light visible to the human eye under magnification, whereas the phages that attack it are a tenth of that size, or a hundred times smaller than the smallest thing we can see. Only with the invention of the transmission electron microscope, in the 1930s, did phages become visible, but because the first images were published in Nazi Germany, it was years before British and American scientists saw them. Even today, most scientists "see" a phage only by the destruction it has wreaked on bacteria in a Petri dish—clear, glassy zones of death scattered across a soupy, yellowish microbial lawn.

In the 1930s, d'Hérelle, who was sympathetic to Communist ideals, was invited by Stalin to help establish a center for phage-therapy research in Tbilisi, which was in the Soviet republic of Georgia. During the Second World War, Soviet and German military medics carried vials of phages as part of their field kits to prevent infection of wounds and burns. That connection with America's adversaries made phages seem ideologically suspect to many in the West. As the medical historian William Summers has written, phage therapy acquired a "Soviet taint" in the postwar period, becoming "scientifically unsound because it was politically unsound."

Still, as late as 1961, phage therapy had some American adherents, including Elizabeth Taylor, who received a dose of staph bacteriophage when she developed near-fatal pneumonia during the filming of "Cleopatra" and needed an emergency tracheotomy. By then, however, phage therapy had been superseded by penicillin, which had become widely available in the West after the war and quickly established itself as the preferred treatment for bacterial infections. Doctors in Eastern Europe continued to prescribe phages—delivered both topically and orally in powders, sprays, and syrups—but their counterparts on the other side of the Iron Curtain had, for the most part, barely even heard of them. Phages were still studied—Francis Crick and James Watson, two of the discoverers of the double-helix structure of DNA, both conducted phage research—but they were not part of modern medicine in Western Europe and the United States.

Give at least two reasons why phage therapy is only now getting attention in the United States

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When a Virus is the Cure Capture Sheet

Continued

The rise of antibiotic-resistant bacteria was predicted by Alexander Fleming, the Scottish bacteriologist who discovered penicillin. In 1945, just seventeen years after his accidental breakthrough, he warned, "There is the danger that the ignorant man may easily underdose himself, and by exposing his microbes to nonlethal quantities of the drug, make them resistant." As early as 1947, penicillin-resistant staphylococcus bacteria were found in hospitals in England, but few heeded Fleming's warning. Antibiotics were systematically overused and abused (including as a growth aid in factory-farmed livestock), giving rise to a microbiological arms race in which bacteria mutated new forms of resistance and scientists raced to develop powerful new classes of antibiotic. To make matters worse, fears of antibiotic resistance have, in recent decades, created a perverse incentive in medical research: new antibiotics, to remain effective, must be used sparingly, as so-called antibiotics of last resort. As a result, it is almost impossible to recoup the cost of developing them. No significant new antibiotics have been introduced since the 1980s, and, in 2001, the World Health Organization issued an urgent call-to-action to tackle antibiotic resistance. Phages were ready for their renaissance.

In November, 2015, Steffanie Strathdee, an infectious-disease epidemiologist at the U.C. San Diego School of Medicine, went on a vacation to Egypt with her husband, Tom Patterson, a professor of psychiatry. After visiting the pyramids, Patterson, sixty-eight at the time, became violently sick with what they at first assumed was food poisoning. But Egyptian doctors gave him a diagnosis of acute pancreatitis, and he was medevaced to Frankfurt, where tests revealed that he also had an abscess infected with a deadly, drug resistant strain of *Acinetobacter baumanni*i. Doctors tested his infection against fifteen powerful antibiotics, but only three had even a slight effect. Another air ambulance brought Patterson home to San Diego, where, within weeks, his infection evolved immunity to those three antibiotics, too. Patterson's organs had begun to fail—first his heart and his lungs, and soon, it seemed, his kidneys—and he went into a coma. By the third week of February, 2016, his doctor, Robert Schooley, warned Strathdee that they were out of options.

Searching the biomedical literature for alternative treatments, Strathdee found a reference to phage therapy. She and Schooley, a human virologist by training, started contacting phage researchers around the world to see if any of them had a virus that might kill Patterson's bug. They received phages originally isolated from sewage plants, Texas dirt, and lagoons of swine and cattle manure; colleagues then grew them in bulk and purified the resulting solution. Schooley received special approval from the FDA. to inject some phages into the plastic tubing draining fluid from Patterson's abdominal cavity, near where the infection had originated, and to pump others directly into a vein. Three days later, Patterson emerged from his coma; after a few months, he was discharged, his infection entirely eradicated.

As Patterson underwent months of physical therapy and rehabilitation, Strathdee and Schooley began publicizing his case, describing it in a scientific paper, giving talks, and providing expert testimony to the National Institutes of Health. In July, 2018, they founded the first phage-therapy center in North America, the Center for Innovative Phage Applications and Therapeutics (IPATH), at U.C. San Diego, and began to build a library of phages. Patterson and Strathdee published a joint memoir about his miraculous recovery, and, as word started to spread, emails, calls, and Facebook messages began to flood in from people desperately hoping that phages could help their loved ones too. It was Patterson's case that Joseph Bunevacz's daughter had heard about, and late last year Strathdee promised to take me along on her next phage-trapping expedition as part of a national search to identify a phage that could kill Bunevacz's pernicious *E. coli*.

Finding phages is not in itself particularly challenging: The average teaspoon of seawater holds five times more phages than there are people in Rio de Janeiro; for every grain of sand in the world, there are a trillion phages. But the best place to find phages that will kill drug-resistant bacteria is where people or animals have shed them—in other words, sewage.

Why are sewage treatment plants and lagoons of swine and cattle good places to search for phages?

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When a Virus is the Cure Capture Sheet

Continued

The timing of a successful phage hunt in Southern California is thus strongly correlated with rainfall. I drove to Carlsbad, just north of San Diego, to meet Strathdee and Patterson for a day of phage hunting.

We filled vials with dubious brown liquid from the end of a rusted pipe, from water that had a coyote turd floating in it, and from the rotting, shrimp-scented swampy edges of the slough. We labeled each sample with a date and a number, and dropped them in Ziplock bags in the cooler. Then she and Patterson drove home, and I took our spoils to U.C. San Diego to meet Hedieh Attai, a postdoctoral researcher.

Attai keeps a freezer of *E. coli*, *Enterococcus*, and *Pseudomonas*—three of the six pathogens that together cause most hospital-acquired infections. Wearing a lab coat, goggles, and gloves, she put a dish of nutrient-rich jelly on a turntable and then, in a process that resembled coating a frying pan with oil, swirled it to distribute a layer of pathogenic *E. coli*. Elsewhere, our samples were sucked through a filter with pores small enough to remove any bacteria, leaving only the phages. The previously murky liquid came out crystal clear—it looked good enough to drink. "I can't let you do that," Attai said, with a nervous laugh. She did, however, let me draw the phage samples into a syringe and squirt a series of identical droplets onto the bacterial film.

If none of the phages we'd found were capable of attacking these particular bacteria, the pathogenic microbes would continue growing undisturbed. But, if the liquid contained a single phage that was a match for this particular host, that phage would bind to the bacterial cell membrane and insert its genome into the fluid-filled interior. Once inside an *E. coli* cell, the phage would take over, mimicking and exploiting the bacterium's own signaling pathways in order to force the cell's protein-manufacturing machinery to start printing out copy after copy of the phage genome instead. Eventually, the *E. coli* cell would become so stuffed with phage copies that it would burst, releasing a horde of phages ready to invade the next bacterial cell. We would know in a day or two if our phage had been successful by the appearance of a circle of dead microbes puncturing the thick layer of *E. coli*.

How is this similar to using antibiotics?

1. They both attack the cell wall or cell machinery of the bacterium.
2. They are both chemicals.
3. They can both kill viruses effectively.

Schooley's major challenge has been securing a phage supply. "We could have started it two and a half years ago if we had a phage source," he said. The pandemic has delayed the trial yet further. In the meantime, a handful of labs and small startups volunteer their time and their phage libraries to help treat sick patients; finding an institution or a company that is willing and able to invest in the basic clinical trials needed to learn how phages work has been all but impossible.

Forest Rohwer, a microbial ecologist at San Diego State University, pointed to a more fundamental problem. In a dynamic ecosystem, whether a coral reef or our bodies, enemies and friends are situational rather than static. Indeed, phage viruses are responsible for creating the majority of pathogenic bacteria in the first place, thanks to their ability to move genes around. An *E. coli* bacterium is usually harmless until it acquires virulence genes from an invading temperate phage. A cholera outbreak is both triggered by phages and halted by them: one kind of phage donates a virulence gene to cholera bacteria, causing it to expand its range, only for another kind to hijack those newly vulnerable pathogenic bacteria to make copies of itself. Sick or healthy humans are just a side effect. Although Rohwer is excited about phage's therapeutic possibilities—his lab purified part of Tom Patterson's phage cocktail—he worries that our ambitions to manipulate an entire ecosystem within the human body might overstep our abilities, and that the unintended consequences might be as unwelcome as the pathogenic bacteria itself. "They can kill you, no problem," he said. "You get the wrong phage and the right bacteria and you're dead."

How is phage therapy potentially dangerous?

1. The phages can get into human cells.
2. The phages cause mutations in the bacteria they infect.
3. The phages can get into the water supply and infect other humans.

Phage therapy thus continues to be a boutique affair—just a few patients, each treated with a personalized phage cocktail scavenged from moldy eggplants, cesspools, and pig farms. It's also hit-and-miss: the phages that Strathdee and I collected at Batiquitos Lagoon turned out, unfortunately, not to be a good match for Joseph Bunevacz's infection. There was better news from Baylor College of Medicine where researchers had isolated phages that were active against Joseph Bunevacz's *E. coli* infection. As Southern California emerged from late-spring rains into a dazzling superbloom, Filomena texted me a photo of the couple embracing on a hillside blanketed with poppies. As it turned out, the coronavirus outbreak was about to slow everything down, and it was late fall before his treatment received FDA. approval. This month, Bunevacz should finally be able to start his phage therapy. "It's a beautiful life," he said when I met him. "And I'd like to push it a little longer."

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Clinical Trials Gone Wrong Reading

Directions
Highlight and annotate the following reading.

Clinical Trial Gone Wrong

Source: *Top 10 Clinical Trials That Went Horribly Wrong*

Annotations

Without clinical trials, no one would know if medicines were safe. The vast majority of the time, these trials go well, and the medicine is approved for general use. But every once in a while, a clinical trial goes wrong due to companies' mistakes. For example, in January 2016, French company Biotrial failed to acknowledge their new drug's pre-trials, which killed several dogs and left others with brain damage. However, the trial was still conducted on humans and made six out of 128 volunteers become sick and go to the ER. Along with ignoring pre-trials, companies can also have prior knowledge that the trial may have negative consequences, such as the gene therapy clinical trial in 1999. One patient, Jesse Gelsinger, was in the final group of patients, and every group before him had suffered severe reactions to the drug. Yet the study continued and Gelsinger's symptoms ranged from jaundice, to organ failure, and eventually to brain death as a result.

Another factor that can make a trial go terribly wrong is the withholding of information to its patients, such as Anil Potti's miracle cancer drug in 2015. At the time, Potti was found guilty of including false data in a manuscript, nine papers, and a grant application, so the results of his studies were invalidated. However, one patient, Joyce Shoffner, still went through Adriamycin-Cytoxan (AC) chemotherapy to cure her breast cancer, only to be told two years later that the study's results had been invalidated due to Potti's involvement. Today, she does not have breast cancer, but she has blood clots and diabetes caused by the AC regimen, as well as post-traumatic stress disorder resulting from the trial itself.

Lastly, companies can have malpractice in their trials, such as the New York Lidocaine Disaster of 1996 where one patient, Hoi Yan "Nicole" Wan, did not know that the researchers took far more cell samples than originally indicated. As they took more samples from her lungs, they increased the dose of her anesthetic, Lidocaine, far above the levels approved by the FDA. An autopsy revealed that lethal levels of Lidocaine had caused her heart to stop beating and the rest of her body to fail along with it. Similarly, in the Elephant Man Trial in 2006, when eight men began writhing in pain and vomiting after being given their doses. One of the participants lost his fingers and toes while another's head swelled up so large that his girlfriend teased him about looking like an elephant. The timing of the dosage made it dangerous because researchers spent 90 minutes slowly injecting animals with the drug, but took only six minutes to inject it into humans.

These particular clinical trials show how important clinical trials are in order to get a drug approved by the FDA. However, these trials are simply the rare cases of clinical trials going horribly wrong. With careful practice and observations, these trials could have been easily avoided and be part of the vast majority of clinical trials that are successful.

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Phage Therapy Clinical Trial Overview

Directions

In groups, use the following overview of the PHAG-O-HEAL clinical trail to complete the Clinical Trials for a New Phage Therapy Capture Sheet.

Evaluation of Phage Therapy for the Treatment of Antibiotic-Resistant Bacteria Infections in Patients

Condition: What is the problem?	Antibiotic-resistant bacterial infection
Intervention: What options are there to solve the problem?	Standard of care (what is currently prescribed): Antibiotic Cocktail—all patients
	Phage Drug: *P. aeruginosa* Phages cocktail—some patients
	Phage Drug: *E. coli* Phages cocktail—some patients

Brief Summary

The objective of PHAG-O-HEAL is to evaluate tolerance and effectiveness of local bacteriophage treatment of septic (whole body) infections in patients.

Study Type	Interventional
Study Type	Randomized
Estimated Enrollment	2,000 patients
Eligibility	Must be 18 years or older (adult), open to all sexes

Detailed Description

HAG-O-HEAL is a clinical trial randomized, multicentric, open-label, standard-of-care-controlled (Antibiotic Treatment) aiming at assessing tolerance and efficacy of local bacteriophage treatment of septic infections due to *E. coli* or *P. aeruginosa* in septic patients using Pherecydes Pharma anti-*E. coli* and anti-*P. aeruginosa* bacteriophage cocktails. This project involves seven clinical sites in the United States.

Outcomes Measured: what data will be collected	Time for bacteria reduction adjusted on antibiotic treatment (Time Frame: 7 days)
	Assessment of tolerance of treatment (Time Frame: 21 days)
	Incidence and delay of infection reduction (Time Frame: 7 days)

Criteria

Inclusion Criteria	Exclusion Criteria
All sexes	Pregnant or breastfeeding woman
Adult Informed consent obtained from patient or next of kin	Intercurrent condition requiring a treatment, which may interfere with analysis results: such as high dose of chronic corticotherapy, immunosuppressive medication, oncologic chemotherapy
In-hospital patient treated for bacteria resistant to antibiotics	Patients included in an interventional research protocol with therapeutic intervention still ongoing upon inclusion time or having participated in anti-infective drug trials during the previous month
Documented infection of *E. coli* or *P. aeruginosa* of any resistance profile, as determined by positive fecal sample	Patients for whom treatment limitation or withdrawal during study period is considered
Treated by antibiotic cocktail	Allergy to antibiotics

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Clinical Trials for a New Phage Therapy, Part 2

Directions
In groups, follow the steps below to take the role of Tom's wife, Steffanie, in deciding if she should enter him into the PHAG-O-HEAL clinical trail.

1. Read and reflect on the background information below.

> Clinical trials for phage therapy have been limited to a few people and cases so far. One reason for this is because antibiotics are more easily available and are safer to use. Remember, phages are 'alive' and can mutate, or change, over time, which would affect the bacteria they are targeting. Per the FDA, the risk is not worth the reward, but that may change with the looming antibiotic crisis. According to the *CDC*, more than 2.8 million antibiotic-resistant infections occur in the United States each year, and more than 35,000 people die as a result. The national cost of these infections is more than $4.6 billion annually.

2. Recall the *How Sewage Saved My Husband's Life from a Superbug video* from Day 1 that was paused at 06:00. Dr. Steffanie Strathdee, Tom's wife, finds a clinical trial called PHAG-O-HEAL that might work for Tom.

3. Read the *Phage Therapy Clinical Trial Overview* and help Steffanie understand all the information about this clinical trial to determine if Tom should be included. Note that *E. coli* and *P. aeruginosa* are two bacteria that can be resistant to antibiotics.

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Clinical Trials for a New Phage Therapy, Part 2

Continued

4. Write a definition (in your own words) and include a picture for following vocabulary terms using the *Glossary* from *ClinicalTrials.gov*.

	Word	Definition	Picture
1	Double-blind		
2	Randomized		
3	Open-label		
4	Multicentric		

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Clinical Trials for a New Phage Therapy, Part 2

Continued

	Word	Definition	Picture
5	Efficacy		
6	Inclusion Criteria		
7	Exclusion Criteria		

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Clinical Trials for a New Phage Therapy, Part 3

Directions
Select three of the following questions and use the information from the reading to answer them.

1	What is being studied?
2	What possible interventions might I receive during the trial?
3	Who will know which intervention I receive? Will I know? Will the research team?
4	What will I have to do?
5	What tests and procedures are involved?
6	Will hospitalization be required?
7	How long will the study last?
8	What type of long-term follow-up care is part of this trial?

#	Your Answer

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Clinical Trials for a New Phage Therapy, Part 4

Directions

Use the following information to help Steffanie determine if she should enroll her husband in the trial.

1. For each indicator, consider why it is important to ensure these criteria are met.

   Source: *Study Management—Clinical Trial Resources—Clinical Trials Resource Center*

	Indicator(s)	Criteria	Why is it important to ask this question?
A	Informed Consent and Documentation	Is it documented that the study has been explained and signed by the participant and/or legally authorized representative allowing for the opportunity to ask questions?	
B	Eligibility Criteria	Has the participant met all Inclusion Criteria and Exclusion Criteria for the study?	
C	Prohibited/Concomitant Medications	Is the participant taking any prohibited medications? If yes, was this finding documented and the PI notified?	

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Clinical Trials for a New Phage Therapy, Part 4

Continued

2. Should Tom participate in this clinical trial? Explain your reasoning.

3. Tom, of course, is not the only person who may or may not participate in this trial. Check out some of the ideas listed in *The Complete Guide to Remarkable Patient Engagement With Clinical Trials* from MDGroup. How can a more diverse patient group be engaged and recruited in this clinical trial? Choose one idea to expand on.

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Career Profile

Research Fellow

Ariangela J. Kozik, PhD
Research Fellow at
University of Michigan
Medical School
Division of Pulmonary
and Critical Care

What is your current role, and how did you get there?

I am currently a research fellow at the University of Michigan Medical School, in the division of Pulmonary and Critical Care. I analyze samples from the airways of asthma patients to understand how the respiratory microbiome is involved in the presentation and pathogenesis of asthma. As a kid, I loved any and all school projects. I was also very curious, always asking questions about everything and always reading. I loved to do mini-experiments like making homemade slime, lava lamps, and growing crystals. The science fair was one of my favorite times of the school year. During my research for a science project in elementary school, I read a lot of books and articles about bacteria and antibiotics, and that was when I first started to really get interested in microbiology. When I started college, I planned to major in psychology and minor in gender studies, with the intent to go into neuropsychology in graduate school. However, during freshman year I had the opportunity to apply to a discovery-based science research course called SEA-PHAGES (Science Education Alliance-Phage Hunters Advancing Genomics and Evolutionary Science). The program involves looking in the soil for bacteriophage (viruses that infect bacteria), and teaches concepts of microbiology and genomics through hands-on learning experiences. I was fascinated by phage biology, the concept of microbiomes—being surrounded by a universe of microorganisms we depend on but can't even see without technology, and the hands-on approach to learning. I switched my major to biotechnology, added some computer science and microbiology classes, and started to learn basic programming skills. In graduate school I decided that microbiome research was what I wanted to devote my career to, and that led me to where I am today.

What skills do you use on a daily basis?

One of the most important skills I use daily is my knowledge of the programming languages R and Python. I use them every day in my work as I analyze genome sequence data. Another important skill is time and project management. I have a lot of projects at a lot of different stages going on at the same time. I also participate in several project teams. Each has its own goals, resources, and timelines so being able to schedule my workday around the needs of each project/team, prioritize when necessary, and plan my efforts in advance is really critical to sustained productivity and keeping stress levels down.

What skills do you use on a daily basis?

I LOVE asking questions to find answers to what we don't know. I think it is the most thrilling thing to be working on the edges of current biomedical knowledge. To be able to come up with ideas about how we think something works and then test whether or not that is true, to be able to look at what we think we know and why we think we know it, and see if we come to the same conclusion—that is fascinating to me and I love that aspect of what I do. The most challenging thing is pushing through times with limited resources and constantly thinking about funding to keep your research going. It takes a lot of mental and creative energy to prepare funding proposals, navigate feedback and make revisions. Having a supportive mentorship team to help work through those issues and improve proposal-writing skills is really important.

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Career Profile
Continued

What was your favorite subject in high school, and why did you love it?

This is hard because I enjoyed school in general. I loved science, but I think my favorite subject was music. I was in Orchestra and Band. I am a very creative person so it was a nice change from the rest of the things I was learning in school. Music is its own language, with notation and rules and distinct ways different instruments participate to create a blended sound that can evoke emotion or change a mood in a matter of moments. It teaches you to listen in a different way, and some of the skills I developed as a musician have been important to my career as a scientist.

If you could have any superpower, what would it be?

Teleportation

If you could instantly learn any language, which would you choose and why?

Mandarin. I studied Mandarin in college, and the hardest part was getting the tones right. If I could have snapped my fingers and instantly known them, I absolutely would have. For now, I will keep practicing.