

The Future of Phage: Ethical Challenges of Using Phage Therapy to Treat Bacterial Infections

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For over a century, scientists have run experiments using phage viruses to treat bacterial infections. Until recently, the results were inconclusive because the mechanisms viruses use to attack bacteria were poorly understood. With the development of molecular biology, scientists now have a better sense of how phage work, and how they can be used to target infections. As resistance to traditional antibiotics continues to spread around the world, there is a moral imperative to facilitate research into phage therapy as an alternative treatment. This essay reviews ethical questions raised by phage therapy, and discusses regulatory challenges associated with phage research, and phage treatments.

Introduction

Tom Patterson, an HIV researcher at UC San Diego, was vacationing in Egypt in 2017 when he was infected with a bacterium resistant to standard antibiotics. After he fell into a coma, he was flown back to San Diego where colleagues obtained approval from the Food and Drug Administration (FDA) to try a last-resort therapy that uses bacteria-eating viruses called bacteriophage. Phage therapy worked, and Professor Patterson returned to his job later that year (Schooley *et al.*, 2017; Strathdee and Patterson, 2019).

Phage were discovered in 1915, but largely ignored in the West with the advent and mass production of antibiotics in the 1920s (Salmond and Fineran, 2015). In Eastern Europe, phage have been used to treat bacterial infections since they were discovered. But their efficacy remained uncertain until scientists showed how phage target-specific bacterial receptors, and how they interact with the human immune system.

Viruses and bacteria co-evolve in ways that are either antagonistic or mutualistic. Some phage viruses invent ways of exploiting bacterial hosts and making more copies of themselves. Bacteria respond with new ways of protecting themselves from viruses. Other phage inadvertently *benefit* bacteria by donating genes that confer resistance to antibiotics, or resistance to other phage viruses. For example, sometimes ‘temperate’ phage, which temporarily integrate their genes into bacterial chromosomes, actually protect bacteria from other viral

invaders, or from antibiotics that would normally harm them (Haaber *et al.*, 2016). So, although phage therapy can be an effective alternative to antibiotics, it can also make bacterial infections *worse* by increasing resistance to antibiotics if they are not appropriately selected and harvested.

This essay reviews the prospects of using phage therapy to treat bacterial infections, especially those resistant to antibiotics. It describes antibiotic resistance as a public health problem; considers the moral responsibility we have to address the problem; recommends some legal channels for speeding up research and development of phage therapy; and discusses the challenge of obtaining consent to the risks associated with phage therapy.

Antibiotic Resistance and Public Health

The use of antibiotics rewards strains of bacteria resistant to antibiotics. Bacteria can acquire resistance through genetic mutation, by the lateral transfer of genes from other bacteria, or from phage that carry antibiotic resistance genes. Any particular person’s use of antibiotics is unlikely to induce a deadly strain of resistant bacteria to evolve—or spread. But when we add up our aggregate use of antibiotics in patients and in agriculture, individually innocent actions contribute to a process that results in grave collective harms in the form of bacterial infections that are difficult or impossible to treat.

doi:10.1093/phe/phaa003

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Antibiotic resistance is a public health problem. When physicians treat a knee injury or a bout of cancer in one of their patients, these are cases of *private* health care, since they primarily help the patient heal, and the patient has no real effect on the health of his community.¹ But when a physician prescribes antibiotics, or a pharmaceutical firm develops new treatments for infectious diseases, these are clear cases of *public* health because people with infections pose serious health risks to the broader population. In other words, the emergence of antibiotic resistance and the development of new kinds of treatments for infections are public health problems that demand moral solutions because they represent situations in which each of us acting alone can produce a worse outcome than all of us acting together.

Examples of antibiotic-resistant infections include drug-resistant tuberculosis, staph and gonorrhea. It has been estimated that about 700,000 people around the world die of antibiotic-resistant infections, and this number is expected to rise dramatically in the coming decades (O'Neill, 2016).

Although the casualties from resistant strains of bacteria are scary, antibiotics are still an enormous net benefit. Antibiotics enable us to undergo invasive surgeries, and they extend health and life for many people whose immune system fails to fight off an otherwise deadly infection. It may be useful to think of antibiotic-resistant bacteria as genetic pollution in our common microbial environment.

Local pollution problems can sometimes be solved by social norms rather than laws. Norms may go some way in deterring *patients* from using antibiotics when they are not needed or are unlikely to work well, and *doctors* from prescribing them without first considering other options. If people believe it is shameful to act in ways that contribute to a collective harm—for example, by consuming factory-farmed meat from animals routinely dosed with antibiotics to compensate for crowded conditions—norms may change the way they behave. Information campaigns can also help. Physicians informing patients about the dangers of antibiotic resistance, and the health risks to the patients themselves, appear to have some effect (Gelband *et al.*, 2015).

But information and social norms directed at changing the behavior of patients and physicians have a limited effect in slowing the emergence of antibiotic resistance, especially since the risks to each person of overusing antibiotics are usually small, while the aggregate costs of overusing antibiotics are big. It is not just the *misuse*—but more generally the *total use*—of antibiotics that contributes to resistance. This makes the use of antibiotics fundamentally different than other kinds of

medications. To the extent that some people are less willing than others to alter their use of antibiotics, it is virtually impossible to tackle antibiotic resistance on a national or global scale via voluntary compliance with norms rather than with coercive laws.

One way to frame our moral obligations toward public health problems like antibiotic resistance is with the public harm principle (Gaus, 1998). According to this principle, when the collective harms produced by our individual actions are unlikely to be significantly reduced through uncoordinated choice, we should create public policies that force us to do our fair share in solving the problem.² In the case of antibiotic resistance, this may involve governments requiring prescriptions for patients to access antibiotics, restricting the use of antibiotics in agriculture, and incentivizing the development of new drugs and diagnostics (Anomaly, 2017).

Only developed countries have the resources to invest substantial amounts of money in basic science research. But *all* countries should penalize the indiscriminate use of antibiotics in agriculture and medicine. They should also discourage physicians from prescribing broad-spectrum antibiotics without first diagnosing the particular strain infecting a patient. These practices are understandable ways of saving time and money for individual patients, farmers or physicians. But all of them ignore the social costs of antibiotic resistance. Phage therapy is one of several new approaches to addressing the problem of antibiotic resistance.

Regulatory Challenges

Phage therapy will likely be able to supplement antibiotics, and thereby extend their curative power. The moral reason for governments—apart from private firms—to support phage research is that individual companies have not been willing to invest much in research and development, in part because they are uncertain how they might profit from phage therapy. While pharma firms are good at turning basic science into profitable treatments, they cannot be expected to pour billions of dollars into ventures for which profitability is uncertain.

Many researchers agree that the development of phage therapy has stalled because of ‘concerns over intellectual property protection’ and ‘lack of a predefined regulatory pathway’ (Kingwell, 2015). The FDA in the USA and the equivalent agency in the European Union have already approved using phage for preserving meat (Love *et al.*, 2018). The basic idea is that an innocuous coating infused with phage viruses or phage enzymes can break

up bacterial biofilms on the surface of meat intended for human consumption. Similar topical treatments are likely to be used in hospital cleaning products that are meant to prevent the spread of MRSA by breaking up biofilms. Topical creams with phage are likely to be used on patients to clear up skin infections caused by bacteria before phage are used to clear internal infections (such as tuberculosis), simply because these products are perceived to be less invasive, and therefore less risky.

For phage to be used to directly treat human infections, the FDA first requires researchers to demonstrate its safety and efficacy in clinical trials. But before we get to the stage of clinical trials, it is worth considering how phage might be produced and distributed. One idea is that government entities like the US National Institute for Health and its analogs around the world can create phage libraries, cataloging the large variety of phage, and allowing approved laboratories, hospitals and physicians to use them. Universities and scientific laboratories could also host phage libraries, though it is likely that a few large organizations in countries with stable political institutions will be needed so that a political crisis does not preclude people around the world from accessing phage samples.

The rationale for publicly funded repositories is that private firms have little incentive to assemble data from which they cannot profit, and there's reason to believe making money from phage research will be difficult—especially in the near future—to the extent that it remains a niche treatment. Among the core functions of government is to finance the provision of public goods, including an infrastructure that prevents the spread of infectious disease. Funding phage libraries may be one way of fulfilling this function.

For private firms to invest in profitable treatments, they will need some assurance that the products they create will be protected as intellectual property. An important difference between traditional antibiotics and phage therapy is that antibiotics are compounds with unique chemical structures that can be patented when they are used for a specific medical purpose. In courts around the world, judges have generally declined to allow individuals or firms to patent forms of life, or their constituents, including strands of DNA or RNA. For example, in 2013, the US Supreme Court ruled that single genes or gene sequences cannot be patented, though the European Union passed a law extending patents to genes that are isolated from their natural environment when doing so requires a technical process. But they did not rule out patenting gene sequencing technologies, or taking out patents on altered gene sequences, or novel

methods for *using* existing genes or organisms to treat disease.

The justification for courts refusing to grant patents over organisms or genes is simple. Although we might speed up some genetics research in the short term by rewarding the discovery of new genes or biological processes with patents, the long-term social costs associated with researchers and firms having to pay patent holders every time they use a gene or chemical would be immense (Rosenberg, 2004). The most likely way firms will be able to profit from phage is by tweaking their genome, by creating phage from scratch or by patenting recipes for phage cocktails (Barbu *et al.*, 2016).

There will likely be plenty of opportunities for patenting different recipes for cocktails since both natural and synthetic phage target-specific bacteria, and the bacteria that infect us are constantly evolving. Creating phage from scratch will often be unnecessary, and much costlier than simply taking a particular phage genome and altering it for the specific needs of patients. Modifying existing viruses provides more opportunities for patenting phage treatments than simply creating cocktails of existing phage.

Genetically altering organisms is already big business in agriculture, and many phage researchers agree that it is worth genetically modifying phage for similar reasons, apart from making it profitable. Genetically modified food can be healthier and better for the environment than 'natural' food. An example is staple crops like corn or rice that can be genetically altered to minimize the need for pesticides or to include antioxidants, calcium and other nutrients that are difficult to find in some parts of the world. Similarly, modified phage viruses can increase the efficacy of treatments and decrease the risk of inadvertently spreading resistance genes from one bacterium to another.

Apart from using patents or other forms of intellectual property to incentivize the development of phage therapy, we could offer firms cash prizes or patent extensions on more profitable drugs if they develop socially valuable but individually costly treatments (Spellberg, 2009). Prizes are simply cash payments for the successful production of a novel treatment that targets specific infections that are difficult to treat. Transferable patent extensions grant a time period—say, 5 years—for which a pharmaceutical firm can continue to collect monopoly profits on a drug of their choice. In effect, it is an indirect cash payment to a pharma firm in the form of artificial profit from one drug in exchange for producing another drug.

This model is already employed by some government agencies and public health organizations to coax drug

companies in developing antibiotics that are not profitable, but which have large social value. The best argument against such ‘pull’ incentives is that government agents are not always in a good position to assess how much social value a new treatment is likely to produce, and (in the case of state-funded prizes) how much informed taxpayers would be willing to pay for research into new treatments like phage therapy. This argument, however, also applies to government agents tasked with determining how long patents should be granted, and for what kinds of inventions. While we should be wary of handing over too much discretion to government agents, some discretion may be needed for them to stimulate the creation of new treatments for infectious diseases. Prizes and transferable patent extensions are worth exploring as part of a package of policies that aim to provide pharma firms with greater financial incentives to develop phage treatments.

Treatment Selection

Phage therapy has enormous potential, but unless we use the right viruses to attack a bacterial infection, phage therapy poses risks to infected patients, and to the general microbial environment. A common distinction is between *lytic* and *lysogenic* life cycles. *Lytic* phage viruses invade a bacterium and immediately hijack its reproductive processes to produce copies of themselves. When enough copies of the virus have been made, the bacterium bursts and spreads phage progeny. *Lysogenic* phage viruses invade a bacterium and integrate into its chromosome rather than immediately destroying it. They often then induce bacteria to express new properties—including resistance to invasion by other phage viruses, and resistance to antibiotics (Abedon *et al.*, 2011, Colavecchio *et al.*, 2017). The problem is not that lysogenic phages integrate their genes into human cells, but rather that sometimes when they integrate into bacterial cells they can cause those bacteria to become resistant to antibiotics. In these cases, phage and bacteria act as mutualists toward each other, but parasites toward us.

Unlike lytic phage, lysogenic phage multiply with the bacterial DNA within which it is integrated. At differing rates, integrated phage DNA is excised from the bacterial DNA and can resume replication as an independent entity. During this process, these phage may bring bits of bacterial DNA with them to the bacteria they next infect. These bacteria-derived genetic sequences can encode resistance genes or genes that might make the new bacterial host more pathogenic for their human or animal hosts.

This makes lysogenic phage undesirable for treating infected patients, partly because they act too slowly to be effective, but also because they can make infections worse by increasing bacterial resistance.

The distinction between lytic and lysogenic phage is sometimes oversimplified, since lysogenic phage can become lytic, and *vice-versa*. It is increasingly common to divide phage into *virulent* (lytic) and *temperate* (lysogenic, with a capacity to become lytic) varieties. This language expresses the idea that at any one time a phage might employ the strategy of lysing (killing) the bacteria it encounters in order to spread copies of itself now, or it might employ the lysogenic strategy of ‘hiding out’ in a bacterium’s chromosome, and temporarily waiting to lyse the bacterium and break free to infect other bacteria in the future (Hobbs and Abedon, 2016).

The consensus view is that we should only treat patients with ‘obligate lytic’ phage that are incapable of lysogeny (Loc-Carrillo and Abedon, 2011). Obligate lytic phage can be found in nature, but they can also be synthetically created by minor genetic tweaks to natural phage using CRISPR Cas-9 and other gene-editing systems (Barbu *et al.*, 2016, Brown *et al.*, 2013). The reason to avoid lysogenic phage, or lytic phage that might revert to a lysogenic life cycle, is that this variety of phage acts too slowly to treat acute infections, and can make infections worse by spreading antimicrobial resistance to bacteria.

Any use of phage therapy, or phage enzymes (‘lysins’) to destroy bacteria on human skin or on surfaces where bacterial biofilms form, will eventually generate resistance by bacteria (Gutierrez *et al.*, 2018). This is a natural consequence of the evolutionary arms race between parasitic viruses and their bacterial hosts (Stern and Sorek, 2011). Using phage as one weapon in our medical arsenal against infectious disease should extend the efficacy of standard antibiotics. This benefits everyone to the extent that all of us are susceptible to bacterial infections and may one day need effective antibiotics to cure an infection or prevent infection during surgery. From a social standpoint, research into phage therapy, and its eventual application, is a net good. In economic terms, it is a public good that markets will likely fail to produce at a socially optimal rate.

Still, unless phage therapy is appropriately administered, its use can induce phage resistance and antibiotic resistance, which can harm all of us. According to a recent review, even if we avoid using lysogenic phage to treat infections, we will still get some antibiotic resistance: ‘Phage are responsible for a considerable amount of horizontal gene transfer. . . During the lytic cycle, bacterial rather than phage DNA may be packed into the

phage capsid, producing a transducing particle that upon release from the (donor) host cell can transfer this bacterial DNA to another (recipient) cell' (Rodriguez-Rubio *et al.*, 2017). This bacterial DNA can include sequences that code for antibiotic resistance.

There is no free lunch in nature. Apart from its potential for creating social costs—or *benefits*, depending on how it is used—phage therapy will create challenges for patient consent. This is partly because of the current uncertainty about the precise risks associated with phage treatments. It is also because, unlike broad-spectrum antibiotics, phage tend to narrowly target-specific bacteria, so the wrong cocktail may fail to heal the patient if the wrong diagnosis is given, the wrong cocktail is selected or the delivery mechanism fails.

Consent

Assuming phage therapy is eventually approved for ordinary use by physicians, surgeons and infectious disease specialists in hospitals, patients will face the choice of whether to consent to be infected with 'live' viruses in order to cure or prevent bacterial infections.

Phage can target infections much more precisely than antibiotics. This means that if they are diagnosed correctly and dosed appropriately, patients given phage therapy can recover from infection with essentially no side effects and few risks. By contrast, broad-spectrum antibiotics often alter or compromise a patient's microbiome in a way that phage do not. For example, an increasing number of patients develop difficulties associated with *clostridium difficile* after taking antibiotics. *Clostridium difficile* is an opportunistic pathogen that multiplies rapidly when competing bacteria are eliminated by a patient's use of antibiotics. The consequences of *c. diff* can include long-term damage to digestion and gut health (Brown *et al.*, 2017).

In principle, consenting to phage therapy isn't much different than consenting to a vaccination. When efficacy is high and risk is low, patient consent is fairly straightforward to obtain, even if patients do not understand the precise scientific mechanisms of the treatment. But phage are different than vaccines, and the risks of phage treatment are mostly a function of physician uncertainty about which infection exists, and which phage is appropriate to select as a treatment. For phage therapy to work well, bacterial infections have to be precisely diagnosed (a costly endeavor), the appropriate cocktail of phage must be selected (or engineered), and the treatment must be delivered in a way that is likely to obviate the patient's immune system (Kingwell, 2015).

Informed consent is the bedrock of modern medical ethics (Flanigan, 2017). But patients are notoriously ignorant about the details of infections, and often conflate bacteria and viruses. Moreover, most practicing physicians currently don't know much about phage viruses since research is in its early stages. For robust consent to be given for phage therapy, patients and physicians will presumably have to spend more time discussing the known and unknown risks associated with treatment than they do in simple cases in which antibiotics are selected and administered to treat a normal case of *pneumonia* or *staph*.

For too long we have taken for granted that when in doubt we can prescribe a powerful, broad-spectrum antibiotic, administered intravenously in cases of urgent need. But as bacteria continue to evolve resistance to standard antibiotics, we will need to explore phage therapy as an alternative in some cases. And until we know quite a bit more about phage, consent will be difficult to obtain because the science is complex, the efficacy is not precisely understood, and the treatment is more difficult for physicians to explain to their patients. For these reasons, in the near future phage will likely be used mainly for topical treatment of skin infections, as a way to sterilize food, to clean hospitals and medical devices, and as a last resort treatment when the best available antibiotics fail to cure a patient.

The purpose of this section is not to develop a novel theory of consent, but to highlight how phage therapy may generate unique challenges that differ from more familiar treatments at the stage of clinical trials and in ordinary clinical settings. The challenge stems mainly from scientific complexity and medical uncertainty.

Conclusion

There are good reasons for governments and public health organizations to invest heavily in basic science research surrounding phage therapy, and specifically to develop detailed catalogs of the variety of viruses that kill bacteria. These reasons stem from the minimal assumption that the primary function of government is to supply core public goods for which there is widespread demand (Anomaly, 2015). These public goods include minimizing the spread of infectious disease and preserving the efficacy of drugs that fight infectious diseases.

Governments should finance clinical trials—including 'challenge studies' in which patients with otherwise untreatable infections are given a phage cocktail. They should also subsidize the development of effective diagnostics, since these will not only bolster patient health,

but will also extend the efficacy of already existing antibiotics. Information gleaned from clinical trials will also increase the accuracy of phage treatment, assuming it becomes viable. It is hard to secure patient consent for clinical trials and treatment regimens that involve complex and poorly understood risks. But this is arguably true for much of modern medicine, including novel treatments for cancer. More research will help us better understand the risks and benefits of phage therapy as a tool in the fight against pathogenic bacteria.

Notes

1. Of course, if the community has a socialized health care system, all treatments that are covered by the public health system can be said to impose costs and benefits on other taxpayers. But it is an open question what kinds of health care systems should exist. This is why it is not obvious that fixing a broken bone or treating a bout of cancer is a case of public health, but it is obvious that treating an infectious disease or preventing the emergence of antibiotic resistant bacteria are paradigms of public health (Anomaly, 2011; Horne, 2019).
2. Another way to frame our obligations in cases like this is that when political institutions can provide us with a package of public goods from which each person in a group benefits, and the production of these goods is unlikely to be socially optimal if each person is left to their own devices, we have reasons to support the provision of such goods (Klosko, 1987).

Acknowledgements

I would like to thank Daniel Callies, Dov Fox, Steff Strathdee and Robert Schooley for their helpful comments. Thanks also to Craig Callender for hosting me as a visiting scholar at the Institute for Practical Ethics at UCSD.

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