A New Ph(age) of Antibiotics

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Viruses infect billions of people yearly, seasonal flu is a commonplace occurrence and COVID-19 updates make daily headlines. But not all viruses infect humans. Bacteriophages are viruses that infect bacteria, which could advance medicine by killing antibiotic resistant bacteria.

As the predators of the virus world, bacteriophages are the most abundant creature on the planet and lurk around every corner. Furthermore, they play a major role in regulating natural bacteria populations, with a recent review stating that bacteriophages kill 20-40 percent of all the ocean's bacteria each day, making them an ecological necessity.

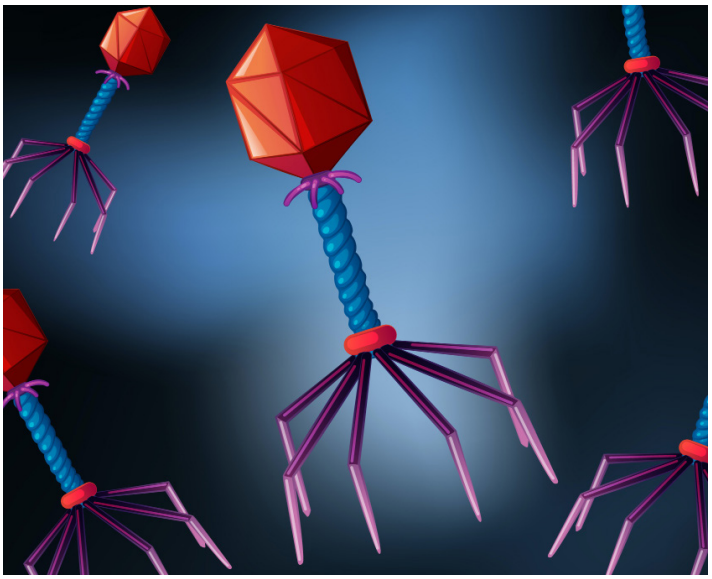
Bacteriophages kill bacteria through two sophisticated mechanisms. The Polish Journal of Microbiology described how all bacteriophages, despite their classification, recognize specific receptors on the outside of prey bacteria before injecting the instructions to create more bacteriophages into the cell.

On one hand, lytic bacteriophages hijack the bacteria's ribosomes — tiny cellular machines that assemble proteins — to produce new phages. When the bacteria can fit no more, the new phages burst forth from the cell into the environment so that they can infect new bacteria.

But some bacteriophages actually take a slower approach, by weaving these instructions to produce new phages into the bacteria's DNA. This information is then passed on to daughter bacteria when the bacteria themselves divide; these phages are called lysogenic bacteriophages. Even so, most phages lie on a spectrum between these two defined groups, with many lysogenic phages switching to a lytic lifestyle under certain environmental conditions.

Bacteriophages have started to move from the environment to hospitals, not as an outbreak but as a treatment. In a race to treat antibiotic resistant bacteria, clinicians can use lytic bacteriophages to treat bacterial infections. Phage therapy involves administering patients with a cocktail of bacteriophages to kill specific bacteria. This therapy is more common in some Eastern European countries, however the United States and the UK do not use phage therapy routinely in their hospitals.

The main reason for this lack of adoption is because western health systems have been fully reliant on antibiotics. Antibiotics are drugs that kill bacteria by targeting universal bacterial mechanisms, such as protein synthesis and cell division. In the past, antibiotics were highly effective at treating bacterial diseases. Over 262 million antibiotic prescriptions were issued in the US in the year 2011 alone.



More recently antibiotic resistance has become a growing concern. The World Health Organisation declared antibiotic resistance a major threat to global health. Laximinarayan et al estimated in their recent Lancet paper that by 2050 antibiotic-resistant bacteria will kill over 10 million people each year, with superbugs, such as *Klebsiella pneumoniae*, already showing resistance to last-resort antibiotics.

Phage therapy can treat some of the most aggressive antibiotic resistant infections. Antibiotic resistant *Klebsiella* kills over 50 percent of its victims but, a recent study found releasing phages into mice lungs effectively clears *K. pneumoniae* infections.

Recent reviews show that multiple human trials have illustrated the effectiveness of phage therapy as an option for treating antibiotic resistant bacteria. A recent article in Nature Medicine commented on how a six week phage treatment saved a young girl's life, after it cleared an initially untreatable *Mycobacterium* infection that developed after she received a lung transplant.

Phage therapy has been suggested as both a conjugative and alternative therapy to antibiotics. The pros and cons of phage therapy often come hand-in-hand. Evaluating both sides helps clarify their potential for being a successful replacement for antibiotics medically in the future.

First, the lock-and-key mechanisms of phages recognise specific receptors to enter bacterial cells. This mechanism allows phage therapy to be a very selective treatment,

reducing its toxicity to human cells. This process also prevents good bacteria within our bodies from being harmed. Patients taking antibiotics, on the other hand, disturb the gut's natural bacterial ecosystem, increasing the chance of multiple infections.

The degree of specificity of phage therapy can also be considered as one of its downfalls. Many scientists have abandoned phage therapy as a realistic potential treatment as the exact strain of bacteria often must be known before administration. Also, phage therapy is considered inappropriate in the case of infections arising from burns, which are often caused by multiple different strains of bacteria.

However, a study published in Cell Reports found that the host range of the *Listeria* phage PSA could be widened by producing new phages with altered receptor binding proteins. The new phages could recognise new receptors that were found on multiple different harmful bacteria and, therefore, were more successful at treating infections.

Analysing phage therapies' benefits in comparison to antibiotics also helps to clear up the picture. Phage therapy has in some cases been seen to have multiple benefits when compared to antibiotics. For example, unlike antibiotics, phage therapy can often be effective after only one dose, as phages are self-replicating; a Nature Paper cites that a single bacteriophage infection often leads to over 200 new bacteriophages being produced.

However, the most drastic advantage is the fact that bacteriophages can penetrate biofilms, which is often a major obstacle for antibiotics. Biofilms are produced by bacteria when they work together to produce a city of bacteria embedded in a secreted carbohydrate and protein mixture which acts like concrete. Hence, protecting bacterial colonies from incoming danger such as antibiotics. But phages possess enzymes which allow them to break down biofilms, leaving the bacteria exposed and easier to kill.

Some phages have even been engineered in the lab to improve their biofilm-breaking capability. For example, an article published in Trends of Microbiology stated how the instructions encoding biofilm disrupting enzymes were incorporated into bacteriophages that could be used to treat human infections. The new engineered phages were able to more effectively lyse bacteria cells within biofilms and expose embedded bacteria in the middle of the colony. Therefore making them more susceptible to both phage and antibiotic treatments.

With a health system that can no longer deal with the increasing number of antibiotic resistant bacteria we must turn to new methods of treating bacterial infections. The antibiotic pipeline is quickly drying up and new diseases demand new treatments. But only future research will tell whether bacteriophage therapy can become a viable alternative.

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