

*Invited Review*

# Exploring Bacteriophage Therapy for Drug-Resistant Bacterial Infections

**Robert T. Schooley, MD**

University of California San Diego

*The golden age of antibiotics, which lasted from the 1930s until 2005, brought a brisk clip of antibiotic discovery and fueled optimism about the victory of modern medicine over bacterial infections. Since then, however, with a stalled antibiotic discovery effort and widespread antibiotic use, antimicrobial resistance has emerged as a major global health threat. Bacteriophages, or phages (literally viruses that infect certain bacteria), have coevolved with bacteria for almost 4 billion years and are the most abundant organisms on the earth. Substantial progress is being made such that selection, engineering, and synthetic production of phages may make it possible for these lethal enemies of bacteria to be harnessed as potent allies in our battle against antimicrobial resistance.*

**Keywords:** bacteriophage, phage, antibiotic-resistant bacteria

## Introduction

The golden age of antibiotics began in the 1930s with the introduction of sulfonamides into clinical medicine and ended in 2005 with the appearance of daptomycin. Since then, no truly novel antibiotics have been brought to the bedside. Throughout the golden age, the brisk clip of antibiotic discovery fueled optimism about the victory of

## Author Correspondence

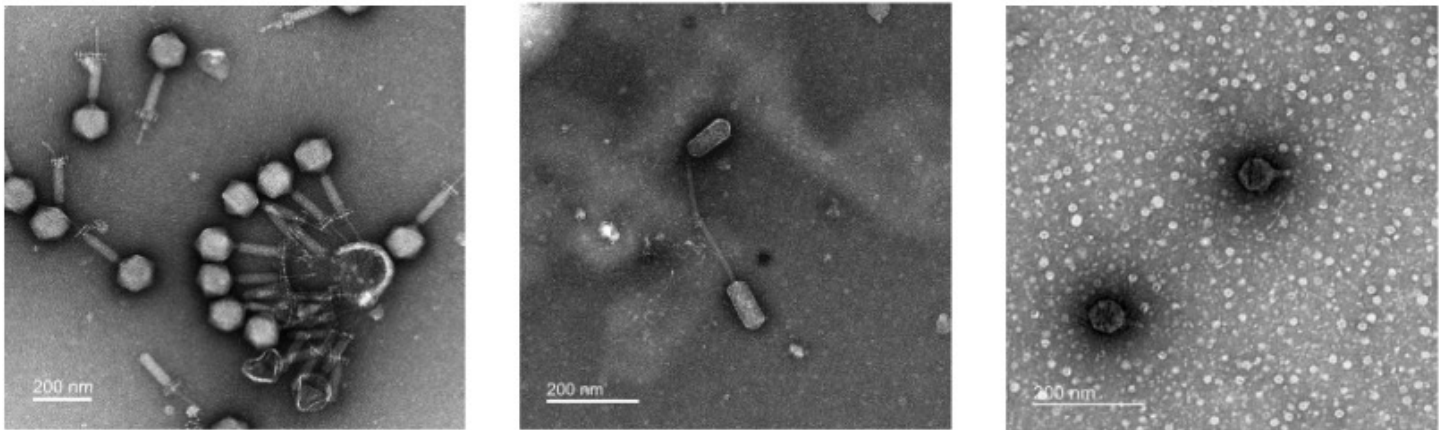
Send correspondence to Robert T. Schooley, MD, Stein Clinical Research Center, University of California San Diego, 9500 Gilman Dr, San Diego, CA, 92093, or email [rschooley@ucsd.edu](mailto:rschooley@ucsd.edu).

modern medicine over bacterial infections. In large part because of the successful antibiotic discovery effort, the growing evidence that resistant microorganisms were emerging at an accelerating rate was not seen as a major threat, and investments in antibiotic discovery waned. With a stalled antibiotic discovery effort and widespread antibiotic use, antimicrobial resistance (AMR) has emerged as a major global health threat over the past 2 decades.

In a comprehensive assessment of the global impact of AMR published in 2022, it was estimated that in 2019, nearly 5 million deaths were associated with AMR and that 25% of these deaths were directly attributable to antibiotic-resistant pathogens.<sup>1</sup> The largest burden of morbidity and mortality from AMR was borne by lower- and middle-income countries, especially those in sub-Saharan Africa. Emerging data indicate that the incidence of AMR has further accelerated during the COVID-19 pandemic.<sup>2</sup> Modeling suggests that AMR-related deaths may increase to 10 million people per year and that the economic costs from lost productivity will be as high as \$1 trillion yearly by 2050 unless current trends are reversed.<sup>3</sup> These alarming trends have stimulated interest in alternative modalities for tackling the problem of AMR. Bacteriophages (or phages), literally “bacteria eaters,” have coevolved with bacteria for almost 4 billion years and are the most abundant organisms on the earth.<sup>4</sup> This article outlines the current evidence that these lethal enemies of bacteria can be harnessed as potent allies in our battle against AMR.

## Phage Discovery and Early Development

Beginning in the last decade of the 19<sup>th</sup> century, researchers noted that there were “factors” in the environment that were capable of lysing bacteria.



**Figure 1.** Electron micrographs of the myoviral (left), siphoviral (center), and podoviral (right) bacteriophage morphotypes. Photographs courtesy of Pooja Ghatbale and David Pride, IPATH Translational Research Laboratory, University of California San Diego School of Medicine.

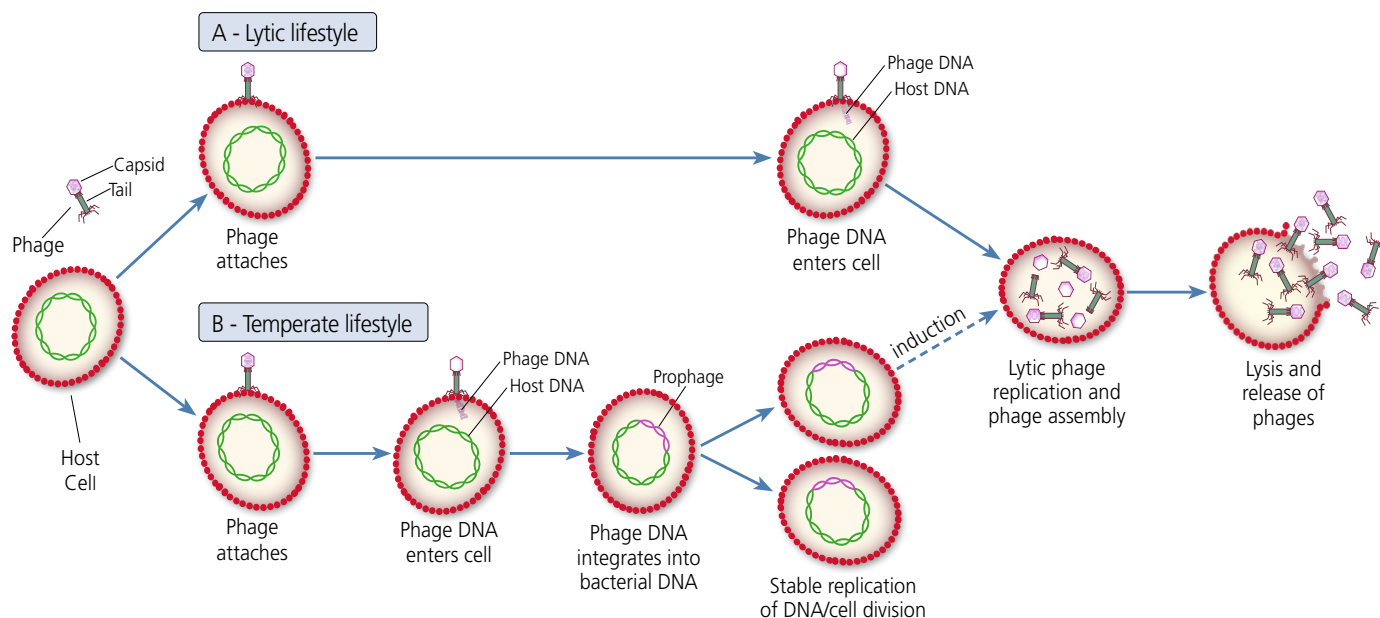
The recognition that these “factors” were parasites of bacteria is attributable to the French microbiologist Félix d’Hérelle, who announced in 1917 that he had discovered an “invisible microbe” that lysed bacteria causing dysentery.<sup>5</sup> This agent could be propagated in bacteria and then passed through filters with pores that were too small for bacteria after the bacterial population had been destroyed. He recognized the potential for these agents to be used therapeutically, and by 1919 he had begun to experiment with them in humans. Although he was convinced that the agents he was working with were reproducing biologic organisms, others believed that the bacterial lysis was being caused by enzymes harbored within the bacteria. With the advent of electron microscopy, Helmut Ruska demonstrated that phages were actually viruses.<sup>6</sup>

The use of phages in medicine became widespread throughout Europe, North America, and the Soviet republics in the 1920s and 1930s and was central to Sinclair Lewis’s novel *Arrowsmith*.<sup>7</sup> A failure to fully appreciate the narrow antimicrobial spectrum of phages and the lack of clinical investigations with rigorous microbiologic underpinnings led to an erosion of the phage fervor in the West. When penicillin emerged during World War II, the broader spectrum of penicillin and the antibiotics that followed resulted in the eclipse of phage therapy by antibiotics in the United States and Europe. Interest in phage therapy continued unabated in Eastern Europe and the Soviet republics, where phage therapy

programs flourished throughout the last half of the 20<sup>th</sup> century.<sup>7</sup> Phage therapy has emerged in the West over the last half-decade as the failure of antibiotics to keep up with AMR has led to a broad awareness that new tools to address AMR are sorely needed. Advances in the understanding of phage biology and improved phage selection and production technologies, coupled with several high-profile anecdotal case reports of the use of phage therapy to cure infections for which antibiotics had failed, have led to a renaissance of interest in phage therapy in the US and Europe.<sup>8,9</sup>

### Phage Biology

Defined most simply, phages are viruses that infect bacteria. They are ubiquitous in nature, immensely diverse, and highly selective in their bacterial prey. The genomes of most, but not all, phages consist of double-stranded DNA. This DNA is tightly packed into the phage capsid and is usually attached to a “tail” of varying length (see Figure 1). The tips of the tail bind with high specificity to structures on the bacterial cell surface and play a major role in defining the breadth (or range) of bacteria that a given phage can infect. Some phages can infect a large proportion of bacterial strains in a given species. These phages are said to have a “broad” host range. Conversely, some phages may infect only a small fraction of bacteria within a species; these are designated as having a “narrow” host



**Figure 2.** Phage life cycle. (A) Lytic lifestyle: Phage attaches to host bacterium and injects its DNA into the cytoplasm. Host metabolic activity is inhibited and phage production is initiated. Following assembly of daughter virions, phage lysins result in disruption of the cell wall and release of progeny phages. (B) Temperate lifestyle: Phage attaches to host bacterium and injects its DNA into the cytoplasm. Early phage gene expression represses the lytic life cycle and enables integration of phage DNA into the genome of the host bacterium or the establishment of a plasmid. This integrated or plasmid “prophage” replicates with the host cell until it undergoes induction and produces lytic phages.

Adapted from Brunton LL.<sup>34</sup>

range. The breadth of host range of a phage is dependent on cell-binding specificities as well as its resistance to intracellular bacterial defenses and is defined by millions of years of coevolution.<sup>10</sup> Phages of certain bacterial species such as *Staphylococcus aureus* may have a broad host range, whereas most phages of other species such as *Acinetobacter baumannii* have narrow host ranges.

Phage replication begins with binding of the phage tail to a ligand on the cell surface (Figure 2). Once the tail has bound to the cell surface, the nucleic acid of the phage is injected into the cytoplasm of the host bacterium and the phage can proceed with 1 of its 2 developmental programs, or “lifestyles.” Based on which of these 2 pathways the phage pursues, a phage is classified as being lytic or temperate. Lytic phages quickly take over the host cell’s metabolic machinery to initiate the phage genome expression, nucleic acid replication, and assembly of hundreds (or more) of progeny phages in as little as 20 minutes. When phage production is complete, lytic proteins are produced and the phages burst through the bacterial cell wall to repeat the process in additional bacteria.

Phages that follow a temperate development program can also follow the lytic pathway; however, at varying frequencies depending on the phage, the bacterium, and growth conditions, the genes essential for the lytic pathway can be turned off and the phage can establish “lysogeny.”<sup>11</sup> In this situation the phage genome becomes a “prophage” and exists within the host bacterium as integrated DNA or as a plasmid. From time to time under the appropriate conditions, these prophages can be activated and resume a lytic lifestyle by creating a burst of progeny phages and lysing their bacterial hosts. When this occurs, phages may incorporate components of the bacterial genome and transfer these genetic elements to bacteria they infect. This transfer of bacterial DNA may enable lateral transfer of deleterious genes encoding antibiotic resistance or pathogenic properties. In addition to the possibility of transferring deleterious genetic elements, prophages may encode repressors that inhibit the ability of lytic phages to infect their bacterial hosts. Because the primary goal of phage therapy is to kill bacterial hosts rather than to transfer genetic material and render bacteria less susceptible to infection

by other phages, temperate phages are not suitable for clinical use.

### **Sourcing and Characterizing Phages and Preparing Them for Clinical Use**

Phages are ubiquitous in the environment and can be found essentially anywhere bacteria are found. Until recently, most phages used in clinical medicine have been sourced and used “as is” from the environment after being prepared for clinical use, although substantial progress is being made in the area of phage engineering and synthetic phage construction.<sup>12–14</sup> Environmental phage searches are generally undertaken by passing extracts of water, soil, or another potential phage source through 0.22- $\mu$ m filters, plating dilutions of the filtrate onto lawns of the bacterium of interest, and looking for holes in the lawn indicative of lytic activity.<sup>15</sup>

The likelihood of finding phages that are active against a given bacterial species may be enhanced by sampling from environmental sources where their host bacteria are likely to be found.<sup>16</sup> Such sources might, for example, include sewage treatment plants for phages active against enteric flora or discarded bandages if the target is a phage with antistaphylococcal activity. Phages can be plucked from regions of the agar where the bacterial lawn has been disrupted, passaged on their intended host for amplification, and then fully characterized. In non-emergency circumstances, this characterization should include whole-genome sequencing to search for genetic sequences indicative of lysogenic potential or genes conferring antibiotic resistance or pathogenetic factors.<sup>17</sup> After passing the genetic search for deleterious sequences, phages are amplified on prophage-free host strains and then purified using approaches that approximate good manufacturing practice conditions.<sup>18</sup> The process of identifying and purifying lytic phages remains one of the rate-limiting features for emergency use of phages. Fortunately, over the past decade a number of well-annotated phage banks have been developed in commercial and academic laboratories that contain phages covering broad spectra of individual bacterial species. When these phage banks can be

used as a starting point, the process of preparing phages for clinical use can be substantially abridged.

### **Principles of Phage Therapy**

The development of the principles of phage therapy is a work in progress. A recent review of animal and human experiences with phage administration identified very few safety concerns.<sup>19</sup> Although much has been learned from case reports, a more systematic approach to phage therapy will require the conduct of rigorous clinical trials based on the same paradigms that have been applied to antibiotic development over the past 80 years.<sup>20,21</sup>

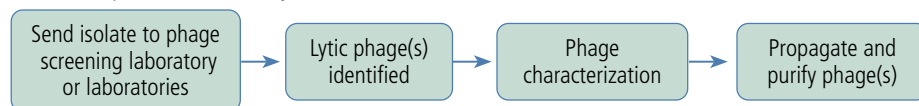
### **Pharmacology**

In perhaps the biggest departure from the experience with traditional antibiotics, phages will propagate on the pathogen at which they are directed once they are delivered to the site of infection. Advances in phage preparation and purification have made it possible to administer phages parenterally, and the clinical use of phages is increasingly shifting to intravenous administration for the treatment of systemic or deep infections.

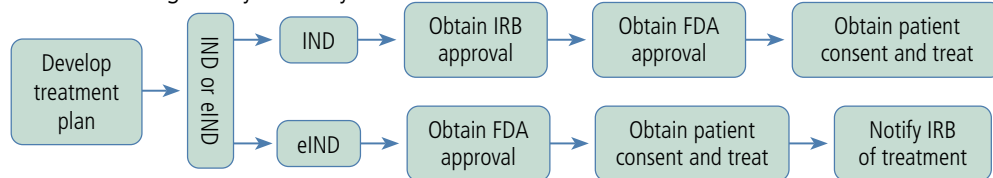
Phages are also administered topically for open wounds and burns, by nebulization for pulmonary infection, orally for gastrointestinal infection, and into the bladder for urinary infections. Phage dosage is expressed as “plaque-forming units” (PFUs), a measure of how many phage particles in a dose are capable of infecting the pathogen of interest in the laboratory. Depending on the dose administered, intravenously administered phages are removed from the circulation by the reticuloendothelial system and sequestered in the liver and spleen over 1 or 2 hours.

Regardless of the route of administration, a primary goal of therapy is to deliver a sufficiently large dose of phage to the site of infection to initiate self-propagating phage replication within the pathogen population. From a practical perspective, most phage regimens feature individual doses in the range of  $10^9$  PFUs per dose. Doses in this range have been associated with treatment success in a number of published case reports. With

## Phase Acquisition Pathway



## Clinical and Regulatory Pathway



**Figure 3.** Steps required to identify and prepare phages for clinical use (top). Steps required for regulatory approval for clinical use of phages in the United States (bottom).

Abbreviations: IND, investigational new drug; eIND, emergency investigational new drug; IRB, institutional review board; FDA, Food and Drug Administration.

current approaches to the removal of endotoxin in the phage production process, higher doses can be difficult to achieve without exceeding US Food and Drug Administration (FDA)-recommended limits on endotoxin administration (5 endotoxin units [EU]/kg/h).

### Phage Resistance

As with all antimicrobial agents, phages can select for organisms with lower levels of susceptibility.<sup>8</sup> Phage resistance can require a substantial tradeoff on the part of the bacterium in terms of fitness. This loss of fitness can come in the form of greatly reduced capsule formation, which can result in less invasiveness and more susceptibility to host immune responses.<sup>8,22</sup> Phages can also be targeted to bacterial efflux pumps that pump antibiotics out of the bacterial cytoplasm. In this case, resistance confers a major disadvantage to the pathogen by re-sensitizing it to antibiotics to which it was previously resistant.<sup>23</sup> Although phages are often administered as “cocktails” to mitigate this challenge, much additional knowledge is required to advance combination design from empiricism to a scientific basis. Solutions proposed include efforts to compose cocktails of phages with different receptor specificity or orthogonal resistance pathways.

### Human Immune Responses to Phages

Phages can be immunogenic and have been used experimentally for decades to study host immune

responses.<sup>24</sup> Humoral and cellular immune responses have been detected in patients receiving phage therapy.<sup>25</sup> Case reports have appeared that link treatment failure to the advent of phage-specific antibodies in an immunocompetent patient.<sup>26</sup> The same phage was used in the treatment of a lung transplant recipient for more than 2 years without immune-based loss of activity.<sup>27</sup>

The frequency and clinical significance of this issue are

not yet fully understood, but currently available evidence suggests that it may be more problematic in the immunocompetent population. Replacement of phages inducing an immune response with phages capable of lysing the target bacterium but not sharing the epitopes of the strain inducing the immune response has been suggested as a strategy to enable extension of therapy should immune responses to the original phage or phages limit their efficacy.

### Phage Susceptibility Testing

Development of tools for the assessment of phage susceptibility in the clinical microbiology laboratory is still in its infancy. The most commonly used approaches to determine phage susceptibility are the agar overlay technique, in which the ability of phages to create visible spots of lysis is assessed, and liquid methods, in which the ability of phages to block bacterial growth is assessed by quantifying bacterial metabolism.<sup>28</sup> The agar overlay method is a classic method for assessing phage susceptibility that has been in use for a century. It requires no specialized equipment, but the readout is subjective. Liquid-based assays can be mechanized for higher throughput and provide quantitative readouts. Efforts to standardize these assays within and across laboratories are in early stages.<sup>29</sup> Very little information is currently available about the extent to which either assay platform predicts clinical activity. As was the case with traditional antibiotics, clinical

correlations will evolve over time in the context of clinical trials and clinical experience.

---

### Practical Aspects of Phage Therapy

Phages have several major properties that make them particularly attractive as antimicrobial agents. Among them is that they are virtually limitless in nature yet highly targeted individually in terms of host range, resulting in potent antimicrobial activity with limited disruption of the microbiome. The ability to disrupt biofilms provides opportunities to dislodge bacteria from implanted prosthetic devices and from biofilms at mucosal surfaces or in wounds.<sup>30</sup> Phages can restore the susceptibility of bacteria to antimicrobial agents by disabling cellular antibiotic efflux pumps.<sup>23</sup>

A wider appreciation of these properties, coupled with advances in biotechnology that have enabled better access to phages suitable for clinical use, has resulted in an accelerating number of case reports of phage therapy in the peer-reviewed medical literature. Case reports of phage therapy that have appeared since 2017 largely reflect these properties.<sup>31</sup> Roughly one-third of the cases have involved implanted prosthetic devices including joints and cardiac devices. Twenty percent of the case reports have focused on pneumonia (mostly involving drug-resistant organisms), and 10% each have been about the treatment of osteomyelitis and urinary tract infections. Modern case series reflecting this diversity of clinical indications for phage therapy are consistent in focus with the distribution of case reports.<sup>32,33</sup> As with other clinical conditions, it is likely that selection bias results in overreporting of courses of therapy that were perceived to be successful. The fact that there has been so much perceived success in these areas, however, has driven interest in clinical trials to the same areas.


When a physician believes that a patient is a candidate for phage therapy, the first step is to find phages that are active against the patient's organism (see Figure 3). This requires that the organism be retrieved from the clinical laboratory where it was isolated. Because clinical laboratories discard organisms relatively quickly after they are characterized, it

is important that the laboratory be asked to save any isolates for which phage therapy might be indicated. The organism then must be sent to a laboratory with access to phages for organisms of that species. This can be a confusing task for physicians who have not been closely following the field; assistance with identifying a laboratory with the correct microbial focus and a willingness to screen the isolate for active phages can be obtained from University of California San Diego's Center for Innovative Phage Applications and Therapeutics (IPATH; <https://med-school.ucsd.edu/som/medicine/divisions/idgph/research/center-innovative-phage-applications-and-therapeutics/Pages/default.aspx>). Physicians and staff members at IPATH are willing to give advice about the suitability of the patient for phage therapy, provide assistance with locating laboratories willing to screen for phages, provide assistance with the regulatory aspects of phage therapy, and discuss possible treatment plans. Over the past 5 years, IPATH has fielded more than 1500 phage therapy consultations.

In the US, phage therapy is still considered to be experimental by regulatory bodies and must be administered under the supervision of the FDA Office of Vaccines Research and Review in the Center for Biologics Evaluation and Research. Individual candidates for phage therapy are treated under the FDA's investigator-initiated investigational new drug (IND) regulations. The FDA should be contacted through its website (<https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/physician-request-single-patient-ind-compassionate-or-emergency-use>) or, in emergency situations, by telephone. The FDA scientist requests information about the case, the phage preparation to be used, and a description of the treatment plan. In emergency situations under the emergency IND (eIND) program, approval can be obtained on the same day. In this case, the patient (or an authorized patient representative) must provide informed consent, but review by a local institutional review board (IRB) is not required. The local IRB must subsequently be notified within 5 days of the initiation of therapy. In less emergent situations, the timeline is a bit longer because more details about the

phage preparation and treatment plan are required and the local IRB must also opine before the initiation of therapy.

## Summary and Conclusions

Over the past several years, phage therapy has become recognized as one of the more promising approaches to the challenge of AMR. Developments in biotechnology have greatly simplified isolation and preparation of phages for clinical use. Phages are being increasingly used in the clinic in the treatment of difficult-to-treat bacterial infections under FDA supervision. Various clinical trials have been launched in the US and Europe that are expected to provide much more detailed knowledge about the principles and practice of phage therapeutics over the years to come. 

Submitted in December 2022 and accepted for publication in December 2022.

*Financial relationships with ineligible companies within the past 24 months: Dr Schooley has served as a consultant to LyseNtech, GSK, and AbbVie, and served on Data Safety Monitoring Boards for Vir Biotechnology and Merck (Updated 3/24/2023)*

## References

1. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet*. 2022;399(10325):629-655.
2. Centers for Disease Control and Prevention (CDC). COVID-19 & antimicrobial resistance. <https://www.cdc.gov/drugresistance/covid19.html>. February 25, 2022. Accessed March 16, 2023.
3. The review on antimicrobial resistance: tackling a crisis for the health and wealth of nations. [https://amr-review.org/sites/default/files/AMR%20Review%20Paper%20-%20Tackling%20a%20crisis%20for%20the%20health%20and%20wealth%20of%20nations\\_1.pdf](https://amr-review.org/sites/default/files/AMR%20Review%20Paper%20-%20Tackling%20a%20crisis%20for%20the%20health%20and%20wealth%20of%20nations_1.pdf). December 1, 2014. Accessed December 28, 2022.
4. Hendrix RW. Bacteriophages: evolution of the majority. *Theor Popul Biol*. 2002;61(4):471-480.
5. D'Herelle F. On an invisible microbe antagonistic toward dysenteric bacilli: brief note by Mr. F. D'Herelle, presented by Mr. Roux. 1917. *Res Microbiol*. 2007;158(7):553-554.
6. Ruska H. Die Sichtbarmachung der bakteriophagen Lyse im Übermikroskop. *Naturwissenschaften*. 1940;28:45-46.
7. Summers WC. The strange history of phage therapy. *Bacteriophage*. 2012;2(2):130-133.
8. Schooley RT, Biswas B, Gill JJ, et al. Development and use of personalized bacteriophage-based therapeutic cocktails to treat a patient with a disseminated resistant *Acinetobacter baumannii* infection. *Antimicrob Agents Chemother*. 2017;61(10):e00954-17.
9. Chan BK, Turner PE, Kim S, Mojibian HR, Elefteriades JA, Narayan D. Phage treatment of an aortic graft infected with *Pseudomonas aeruginosa*. *Evol Med Public Health*. 2018;2018(1):60-66.
10. Hendrix RW. Evolution: the long evolutionary reach of viruses. *Curr Biol*. 1999;9(24):R914-R917.
11. Howard-Varona C, Hargreaves KR, Abedon ST, Sullivan MB. Lysogeny in nature: mechanisms, impact and ecology of temperate phages. *ISME J*. 2017;11(7):1511-1520.
12. Adler BA, Hessler T, Cress BF, et al. Broad-spectrum CRISPR-Cas13a enables efficient phage genome editing. *Nat Microbiol*. 2022;7(12):1967-1979.
13. Marinelli LJ, Piuri M, Hatfull GF. Genetic manipulation of lytic bacteriophages with BRED: bacteriophage recombineering of electroporated DNA. *Methods Mol Biol*. 2019;1898:69-80.
14. Mitsunaka S, Yamazaki K, Pramono AK, et al. Synthetic engineering and biological containment of bacteriophages. *Proc Natl Acad Sci U S A*. 2022;119(48):e2206739119.
15. Jordan TC, Burnett SH, Carson S, et al. A broadly implementable research course in phage discovery and genomics for first-year undergraduate students. *mBio*. 2014;5(1):e01051-13.
16. Clokie MR, Millard AD, Letarov AV, Heaphy S. Phages in nature. *Bacteriophage*. 2011;1(1):31-45.
17. Philipson CW, Voegtly LJ, Lueder MR, et al. Characterizing phage genomes for therapeutic applications. *Viruses*. 2018;10(4):188.
18. Luong T, Salabarria AC, Edwards RA, Roach DR. Standardized bacteriophage purification for personalized phage therapy. *Nat Protoc*. 2020;15(9):2867-2890.
19. Liu D, Van Belleghem JD, de Vries CR, et al. The safety and toxicity of phage therapy: a review of animal and clinical studies. *Viruses*. 2021;13(7):1268.
20. Suh GA, Lodise TP, Tamma PD, et al. Considerations for the use of phage therapy in clinical practice. *Antimicrob Agents Chemother*. 2022;66(3):e0207121.
21. Schooley RT, Strathdee S. Treat phage like living antibiotics. *Nat Microbiol*. 2020;5(3):391-392.
22. Liu M, Hernandez-Morales A, Clark J, et al. Comparative genomics of *Acinetobacter baumannii* and therapeutic bacteriophages from a patient undergoing phage therapy. *Nat Commun*. 2022;13(1):3776.
23. Chan BK, Sstrom M, Wertz JE, Kortright KE, Narayan D, Turner PE. Phage selection restores antibiotic

- sensitivity in MDR *Pseudomonas aeruginosa*. *Sci Rep*. 2016;6:26717.
24. JERNE NK, AVEGNO P. The development of the phage-inactivating properties of serum during the course of specific immunization of an animal: reversible and irreversible inactivation. *J Immunol*. 1956;76(3):200-208.
  25. Dan JM, Lehman SM, Al-Kolla R, et al. Development of host immune response to bacteriophage in a lung transplant recipient on adjunctive phage therapy for a multidrug resistant pneumonia. *J Infect Dis*. 2023; 227(3):311-316.
  26. Dedrick RM, Freeman KG, Nguyen JA, et al. Potent antibody-mediated neutralization limits bacteriophage treatment of a pulmonary *Mycobacterium abscessus* infection. *Nat Med*. 2021;27(8):1357-1361.
  27. Dedrick RM, Guerrero-Bustamante CA, Garlena RA, et al. Engineered bacteriophages for treatment of a patient with a disseminated drug-resistant *Mycobacterium abscessus*. *Nat Med*. 2019;25(5):730-733.
  28. Henry M, Biswas B, Vincent L, et al. Development of a high throughput assay for indirectly measuring phage growth using the OmniLog™ system. *Bacteriophage*. 2012;2(3):159-167.
  29. Cunningham SA, Mandrekar JN, Suh G, Patel R. Preliminary reproducibility evaluation of a phage susceptibility testing method using a collection of *Escherichia coli* and *Staphylococcus aureus* phages. *J Appl Lab Med*. 2022;7(6):1468-1475.
  30. Chang C, Yu X, Guo W, et al. Bacteriophage-mediated control of biofilm: a promising new dawn for the future. *Front Microbiol*. 2022;13:825828.
  31. Strathdee S, Hatfull G, Mutalik V, Schooley R. Phage therapy: from biologic mechanisms to future directions. *Cell*. 2023;186(1):17-31.
  32. Aslam S, Lampley E, Wooten D, et al. Lessons learned from the first 10 consecutive cases of intravenous bacteriophage therapy to treat multidrug-resistant bacterial infections at a single center in the United States. *Open Forum Infect Dis*. 2020;7(9):ofaa389.
  33. Dedrick RM, Smith BE, Cristinziano M, et al. Phage therapy of *Mycobacterium* infections: compassionate-use of phages in twenty patients with drug-resistant mycobacterial disease. *Clin Infect Dis*. 2023;76(1): 103-112.
  34. Brunton LL, Knollmann BC, eds. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. 14th ed. McGraw Hill; 2023.
- 
- Top Antivir Med*. 2023;31(1):23-30  
©2023, IAS–USA. All rights reserved.