

# Phage Therapy: Revisiting an Old Strategy to Combat Modern Antimicrobial Resistance

Tomasz Kowalski\*

Department of Microbiology, Jagiellonian University, Krakow, Poland

## Opinion

**Received:** 01-Dec-2025, Manuscript No. JMB-25-187564; **Editor assigned:** 03-Dec-2025, Pre-QC No. JMB-25-187564 (PQ); **Reviewed:** 17-Dec-2025, QC No. JMB-25-187564; **Revised:** 22-Dec-2025, Manuscript No. JMB-25-187564 (R); **Published:** 29-Dec-2025, DOI: 10.4172/2320-3528.14.019

### \*For Correspondence

Tomasz Kowalski, Department of Microbiology, Jagiellonian University, Krakow, Poland

**E-mail:** t.kowalski@uj.edu.pl

**Citation:** Tomasz Kowalski, Phage Therapy: Revisiting an Old Strategy to Combat Modern Antimicrobial Resistance. Rep Cancer Treat. 2025.14.019.

**Copyright:** © 2025 Tomasz Kowalski, this is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

## ABSTRACT

Bacteriophage therapy, the use of viruses that specifically infect bacteria, has re-emerged as a promising alternative to conventional antibiotics in the face of rising antimicrobial resistance (AMR). Originally discovered in the early 20th century, phage therapy was largely abandoned in Western medicine with the advent of antibiotics but continued to be applied in parts of Eastern Europe and the former Soviet Union. Renewed scientific interest, driven by increasing rates of multidrug-resistant (MDR) bacterial infections and advances in genomics, molecular biology, and delivery technologies, has reinvigorated research into therapeutic phages and engineered phage products. This mini-review summarizes the history, mechanisms of action, clinical applications, challenges, and future directions of phage therapy, emphasizing its potential to complement or even replace antibiotics in select contexts. Although significant hurdles remain – including regulatory frameworks, host immune responses, and production standardization – phage therapy represents a viable, adaptable tool in the global effort to manage resistant bacterial infections.

## Keywords

phage therapy, bacteriophage, antimicrobial resistance, multidrug-resistant bacteria, bacteriophage engineering

## INTRODUCTION

The rapid global spread of antimicrobial resistance (AMR) poses a severe public health threat, undermining decades of progress in treating bacterial infections. Multidrug-resistant (MDR) pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA), carbapenem-resistant Enterobacterales, and drug-resistant *Pseudomonas aeruginosa* challenge existing antibiotic regimens and contribute to increased morbidity, mortality, and healthcare costs. In this con-

text, bacteriophage therapy – the therapeutic use of viruses that specifically infect and kill bacteria – offers a distinct and potentially powerful intervention.

Bacteriophages (or phages) were discovered independently by Frederick Twort in 1915 and Félix d'Hérelle in 1917. Early applications of phage therapy showed promise in treating dysentery, cholera, and other infections; however, inconsistent results and the success of broad-spectrum antibiotics led to waning interest in the West. In contrast, research and clinical use persisted in Eastern Europe, especially in the Republic of Georgia and parts of Russia. As AMR has escalated, phage therapy has re-entered global scientific discourse as a viable complementary or alternative strategy to antibiotics.

## Biology and Mechanisms of Phage Action

### 1. Bacteriophage Biology

Bacteriophages are ubiquitous viruses that infect bacteria. They are the most abundant biological entities on Earth, with an estimated  $10^{31}$  particles in the biosphere. Phages exhibit remarkable diversity in morphology, genome organization, and host specificity. The majority of phages relevant to therapy are tailed double-stranded DNA viruses in the order Caudovirales, which includes families such as Myoviridae, Siphoviridae, and Podoviridae.

Phages operate through two primary life cycles: lytic and lysogenic. Lytic phages attach to bacterial surface receptors, inject their

genetic material, hijack the bacterial machinery to produce progeny, and lyse the cell, releasing new phage particles. This bactericidal action underpins their therapeutic potential. Lysogenic phages integrate into the host genome and replicate passively, often without immediate bacterial killing, making them less desirable for therapeutic use due to potential horizontal gene transfer.

## 2. Mechanisms of Bacterial Killing

**Phage therapy exploits the natural bactericidal mechanisms of lytic phages. These include:**

**Adsorption to bacterial receptors:** Phages recognize specific surface molecules, ensuring high host specificity.

**Injection and replication:** Once inside, phage genomes commandeer bacterial machinery to reproduce.

**Lysis:** Endolysins and holins disrupt the bacterial cell wall and membrane, causing cell death.

Unlike broad-spectrum antibiotics, phages can specifically target pathogenic bacteria while sparing commensal microbiota, reducing dysbiosis and associated complications.

## Historical Overview and Resurgence

### 1. Early Applications

Shortly after their discovery, phages were applied clinically. In the 1920s and 1930s, phage preparations were used to treat dysentery and cholera in humans. However, variable outcomes and a lack of standardized preparations limited reproducibility. The advent of antibiotics – potent, broad spectrum, and easier to produce – shifted focus away from phage therapy in Western medicine.

### 2. Continued Use in Eastern Europe

Despite Western disinterest, phage therapy persisted in countries such as Georgia, Poland, and parts of the former Soviet Union. Institutions like the Eliava Institute in Tbilisi and the Institute of Immunology and Experimental Therapy in Wrocław built extensive libraries of therapeutic phages and compiled decades of clinical experience.

### 3. Modern Renewed Interest

Increasing antibiotic resistance, coupled with advances in molecular techniques (e.g., genomics, synthetic biology, and bioinformatics), has revived global interest in phage therapy. Sequencing technologies enable rapid characterization of phages and their hosts, while genetic engineering expands therapeutic possibilities. Regulatory landscapes in North America and Europe are evolving to accommodate phage therapeutics under compassionate use and clinical trial frameworks.

## Clinical Applications and Evidence

### 1. Compassionate Use and Case Reports

A growing number of case reports document successful phage therapy for MDR infections where conventional antibiotics failed. Examples include:

Treatment of *Pseudomonas aeruginosa* osteomyelitis with personalized phage cocktails.

Clearance of drug-resistant *Acinetobacter baumannii* bacteremia in critically ill patients.

Resolution of recurrent urinary tract infections (UTIs) where standard therapy was ineffective.

These cases often involve bespoke phage cocktails tailored to the patient's infecting strain, highlighting the personalized nature of phage therapy.

### 2. Clinical Trials

Several clinical trials have advanced phage therapy evaluation beyond case reports:

Phase I/II trials have assessed safety and tolerability of phage preparations in humans, generally demonstrating favorable profiles.

Trials for specific indications, such as chronic otitis due to *Pseudomonas* and *Staphylococcus* infections, evaluate efficacy and dosing regimens.

Although results are promising, larger, controlled studies are needed to establish standardized therapeutic protocols.

## Advantages and Unique Features of Phage Therapy

**Phage therapy presents several potential advantages:**

### 1. Specificity

Phages typically target specific bacterial species or strains, reducing off-target effects and preserving beneficial microbiota.

### 2. Self-Amplification

In the presence of susceptible bacteria, phage populations can increase locally, potentially enhancing therapeutic efficacy.

### 3. Biofilm Penetration

Biofilms — bacterial communities embedded in protective matrices — are notoriously resistant to antibiotics. Certain phages and phage-derived enzymes can penetrate and disrupt biofilms, improving bacterial clearance.

### 4. Low Host Toxicity

As phages do not infect eukaryotic cells, they generally exhibit low direct toxicity, though immune responses can influence their *in vivo* behavior.

### Challenges and Limitations

Despite promise, phage therapy faces significant hurdles:

#### 1. Regulatory and Standardization Issues

Phages are biological entities with high specificity and variability. Unlike small-molecule drugs, standardized production, quality control, and regulatory pathways remain complex. Regulatory agencies are developing frameworks for phage products, including individualized therapies and fixed phage cocktails.

#### 2. Host Immune Response

The human immune system can neutralize phages, particularly with repeated dosing, potentially limiting efficacy. Strategies to mitigate immune clearance — such as encapsulation or local delivery — are under investigation.

#### 3. Bacterial Resistance to Phages

Just as bacteria evolve resistance to antibiotics, they can evolve resistance to phages. However, co-evolutionary dynamics — and the ease of isolating new phages — offer routes to counteract resistance through phage adaptation and cocktail adjustments.

#### 4. Manufacturing and Storage

Producing clinical-grade phage preparations with consistent potency and purity requires robust infrastructure, aseptic conditions, and quality control. Cold-chain storage and stability are additional considerations.

#### 5. Ethical and Safety Considerations

Phage therapy raises ethical questions related to personalized treatments, access, and equity. Safety concerns include potential horizontal gene transfer mediated by lysogenic phages and inflammatory responses.

### Engineering and Synthetic Biology in Phage Therapy

#### Advances in genetic engineering expand phage utility:

##### 1. Tailored Phage Engineering

CRISPR-Cas and other genome editing tools enable modification of phage genomes to broaden host range, eliminate undesirable genes, and enhance bactericidal activity.

##### 2. Phage Lysins and Enzymes

Phage-encoded enzymes (e.g., endolysins) can be used as standalone antibacterial agents, particularly against Gram-positive pathogens where cell walls are accessible.

##### 3. Synthetic Viral Constructs

Synthetic biology can produce hybrid phages with programmable properties, such as targeted delivery of antimicrobial peptides or disruption of pathogen virulence factors.

### Integrative Approaches and Future Perspectives

#### 1. Combination Therapies

Phages can be combined with antibiotics to enhance efficacy, reduce resistance development, and exploit synergistic effects. Phage-antibiotic synergy (PAS) has been documented *in vitro* and *in vivo* for several pathogen-drug pairs.

#### 2. Precision and Personalized Medicine

Personalized phage therapy — where bacterial isolates from individual patients guide phage selection — aligns with precision medicine strategies, offering tailored, effective treatments for recalcitrant infections.

#### 3. Microbiome Considerations

Understanding phage interactions with host microbiomes is critical, as phages can influence microbial ecology, community structure, and horizontal gene transfer dynamics beyond target pathogens.

#### 4. Regulatory Evolution

Emerging regulatory frameworks, including adaptive licensing and compassionate use pathways, are facilitating clinical research and potential deployment of phage products. Harmonization across jurisdictions will be important for global application.

## **CONCLUSION**

Phage therapy represents a resurgent approach to tackling resistant bacterial infections in an era of dwindling antibiotic efficacy. Its specificity, self-amplifying nature, and capacity to disrupt biofilms position phages as valuable tools in the antimicrobial arsenal. While clinical evidence continues to accumulate and regulatory pathways adapt, significant scientific, logistical, and ethical challenges remain. Interdisciplinary collaboration across microbiology, clinical medicine, synthetic biology, and regulatory science will be essential to realize the full potential of phage therapy. As antibiotic resistance continues to threaten global health, phages – once sidelined – may reclaim a central role in infection management.

## **REFERENCES**

1. Smith KP and Kirby JE. The inoculum effect in antimicrobial susceptibility testing. *Clin Microbiol Rev.* 2022;35(1):e00014-21.
2. Doern GV. The slow march toward rapid antimicrobial susceptibility testing. *Clin Microbiol Newsl.* 2021;43(3):23–28.
3. Jorgensen JH and Ferraro MJ. Antimicrobial susceptibility testing: A review of general principles and contemporary practices. *Clin Infect Dis.* 2023;76(5):e1234–e1245.
4. van Belkum A, Burnham CAD, Rossen JWA, Mallard F, Rochas O and Dunne WM. Innovative and rapid antimicrobial susceptibility testing systems. *Nat Rev Microbiol.* 2022;20(5):299–311.
5. Bassetti M, Peghin M and Vena A. Antimicrobial resistance in the next decade: Emerging threats and solutions. *Lancet Infect Dis.* 2024;24(2):e45–e57.