https://doi.org/10.35845/kmuj.2025.24069

VIEWPOINT

Bacteriophages: a new weapon against antibiotic resistance

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ABSTRACT

The emergence of antimicrobial resistance (AMR) poses one of the most significant threats to global public health, with projections indicating 10 million annual deaths by 2050 if left unchecked. As traditional antibiotics lose efficacy against resistant bacterial strains, bacteriophages-nature's bacteria-killing viruses-offer a promising alternative therapeutic approach. This review examines the potential of phage therapy in combating antibiotic-resistant infections, highlighting key advantages including high specificity, minimal disruption to beneficial microbiota, self-replication at infection sites, and co-evolutionary potential with bacterial targets. Recent clinical successes, including the landmark treatment of multidrug-resistant Acinetobacter baumannii infection, demonstrate the therapeutic viability of personalized phage cocktails. However, significant challenges remain, including regulatory frameworks, manufacturing complexities, and limited host range specificity. Future directions encompass engineered phages, combination therapies, prophylactic applications, and phage-derived lysins. While not a panacea, bacteriophage therapy represents a crucial tool in our evolving antimicrobial arsenal, offering hope in the post-antibiotic era through innovative approaches to bacterial infection management.

Keywords: Bacteriophages (MeSH); Phage Therapy (MeSH); Antibiotic Resistance (MeSH); Antibiotic Resistance, Microbial (MeSH); Antimicrobial Drug Resistance (MeSH); Antimicrobial Resistance, Drug (MeSH); Alternative antimicrobial agents (Non-MeSH); Bacterial Infections (MeSH); Precision Medicine (MeSH); Biofilm disruption (Non-MeSH); Drug Resistance, Microbial (MeSH); Drug Resistance (MeSH).

THIS ARTICLE MAY BE CITED AS: Malik MMUD. Bacteriophages: a new weapon against antibiotic resistance. Khyber Med Univ J 2025;17(3):374-6. https://doi.org/10.35845/kmuj.2025.24069

INTRODUCTION

In the archives of medical history, few breakthroughs have had the impact of antibiotics. The miracle drugs transformed health care, saving millions of lives, and reshaping human history. But as we grapple with the challenges that our 21st-century medicine brings, we are met with a modern-day disaster that we did not anticipate: the rise of antimicrobial resistance (AMR). That bacteria become resistant to the very drugs that one killed them is simply an inevitable by-product of this hand-off. This is the phenomenon of bacteria adapting to resist the drugs we develop to kill them, and it is on the World Health Organization's list of the top 10 public health threats we humans faces today.[1] Faced with the collapse of our most powerful antibiotics, we are scrambling for new ways to take on these small yet incredibly powerful opponents. Introducing a would-be rescuer against the growing threat: phages, naturally occurring viruses that kill bacteria, nature's own enemies of infectious disease.

AMR poses a grave global health threat. Accelerated by the overuse and misuse of antibiotics, this natural process is reversing progress to an era when common infections were often fatal. The statistics are alarming: AMR directly caused more than 1.27 million deaths worldwide in 2019, and projections estimate up to 10 million deaths annually by 2050 if current trends persist.[2] These figures are summarized in Table I. The cost, of course, is equally staggering, estimates that the global economy will take a $100 trillion punch in the stomach by mid-century if AMR is allowed to run wild.

The consequences of antibiotic resistance are far-reaching beyond infectious diseases. Most modern medical procedures, from organ transplants to cancer chemotherapy, become far too risky without effective antibiotics. The possible fall of contemporary medicine is imminent and this emphasizes the need for alternative strategies for addressing bacterial infections.

Bacteriophages, literally "bacteria eaters" from the Greek, are viruses that specifically target bacteria. The bacteriophage life cycle is illustrated in Figure 1. First explored in the early 20th century, phage therapy was used to treat bacterial infections prior to the advent of antibiotics. But as antibiotics became widespread, phage therapy largely fell out of favor in the West, while remaining in limited use in selected Eastern European countries.[3] Yet now that we are hitting the wall with our antibiotic arsenal, scientists are beginning to return to phage therapy with renewed focus and 21st-century science.

Bacteriophages offer several advantages over conventional antibiotics. They exhibit high specificity, targeting only pathogenic bacteria while sparing the normal flora. At the site of infection, phages are self-replicating and can evolve alongside bacteria, potentially overcoming emerging resistance. Importantly, some phages have demonstrated the ability to disrupt and eradicate bacterial biofilms, which are often highly resistant and difficult to treat.

Recent research has revealed the possibility of phage therapy as a treatment for antibiotic-resistant infections. A pioneering case was reported in a patient with multidrug-resistant Acinetobacter baumannii infection, for whom a tailor-made bacteriophage cocktail was administered with resolution of the infection.[4] The case literally, and several others, have sparked hope in phage therapy as a substitute or complement to antibiotics.

Despite their promise, several challenges hinder the widespread adoption of phage therapy. Regulatory frameworks pose a significant barrier, as phage therapy is inherently

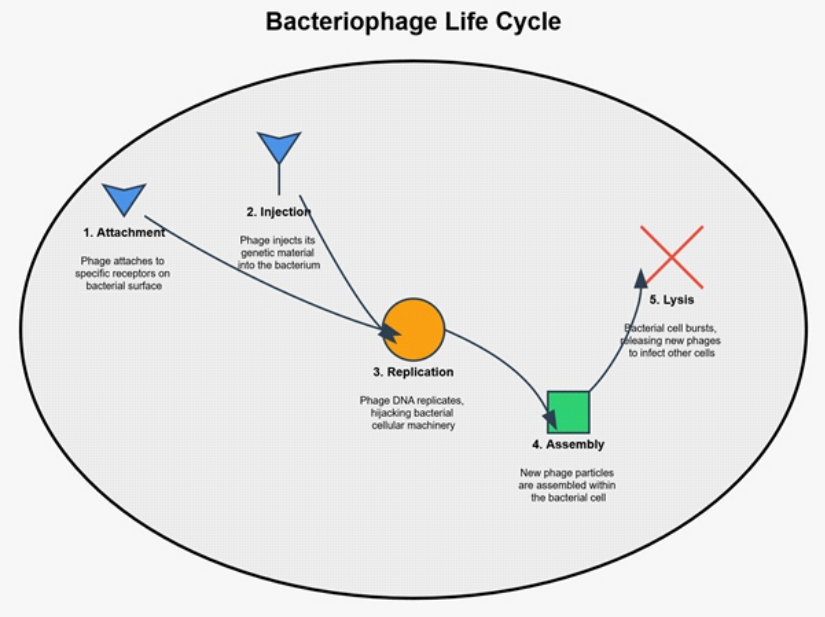

Figure 1: Bacteriophage Life Cycle. This diagram illustrates the key stages of bacteriophage infection and replication within a bacterial host cell (Source: Original illustration based on general phage biology principles)

Table I: Global impact of antimicrobial resistance

Metric	Value	Year
Annual deaths attributable to AMR	1.27 million	2019
Projected annual deaths if AMR is not addressed	10 million	2050
Estimated economic cost	$100 trillion	By 2050

Source: Adapted from Murray CJ, et al., (2022) [2]

Table II: Comparison of antibiotics and phage therapy

Characteristic	Antibiotics	Phage Therapy
Specificity	Often broad-spectrum	Highly specific
Side effects	Can affect beneficial bacteria	Minimal impact on normal flora
Resistance development	Rapid	Slower, co-evolution possible
Manufacturing	Chemically synthesized	Biological production
Regulatory approval	Established pathways	Challenges with current frameworks
Cost of development	High	Potentially lower
Customization	Limited	Highly customizable

Source [3,4]

personalized and current guidelines remain unsupportive of such approaches. Manufacturing and quality control also present difficulties, with standardization of safe and effective phage preparations being complex. Although less common than with antibiotics, bacterial resistance to phages may still occur. Furthermore, the narrow host range of most phages necessitates precise bacterial diagnosis to ensure effective treatment. Key challenges and potential solutions are summarized in Table III.

Nonetheless, studies and clinical trials continue to overcome these constraints and the future of phage therapy in modern medicine looks promising. A few promising directions for the future of phage therapy is developing. Researchers are looking for methods to modify phages, making them more efficient and broadening their hosts spectrum.[5] Some researchers think that combining phages with antibiotics might help increase their effectiveness and limit resistance formation.[7] In addition, phages could be used prophylactically to guard against infection in high-risk situations, such as in people with burns or cystic fibrosis. Phage mediated antimicrobials lysins, enzymes released from phage that rupture bacterial cells, are also being explored for use as independent antimicrobials.[6]

Bacteriophages are looking like a glimmer of hope in a post-antibiotic future. Phage therapy is not a silver bullet, but it does represent an important weapon in our arsenal against drug resistant bacteria. Widely applying the current study to clinic would subject to continued scientific innovations in regulations and public knowledge education.

The discovery of bacteriophages, the forgetfulness, and the possible resurrection provides a good example of the cyclicality of science. Now faced with the rise of antibiotic resistance, we are going full circle and returning to nature's own solution: harnessing these tiny predators to protect human health.

The road ahead is complex, but the stakes are immense. With continued exploration of bacteriophages and innovative scientific approaches, there is hope of reversing the tide of antibiotic resistance and preserving the miracles of modern medicine for future generations. The revival of phage therapy is not merely a scientific endeavor but a testament to human ingenuity and resilience. As research advances and methods are refined, a future where even antibiotic-resistant infections are no longer a lethal threat to human health and safety appears increasingly within reach.

Table III: Challenges and potential solutions in phage therapy development

Challenge	Potential Solution
Regulatory hurdles	Develop new regulatory frameworks specific to phage therapy
Manufacturing complexity	Invest in standardized production methods and facilities
Potential for resistance	Use phage cocktails and leverage phage evolution
Limited host range	Develop rapid diagnostics and personalized phage libraries
Limited stability	Improve formulation and storage techniques

Source [5,6]

CONCLUSION

Phage therapy represents a nature-derived solution to one of modern medicine's most urgent challenges. Despite hurdles in regulation, standardization, and clinical validation, its demonstrated in vivo effectiveness against multidrug-resistant isolates highlights its therapeutic promise. With continued research, regulatory adaptation, and technological advancement, bacteriophages could become pivotal in sustaining effective antimicrobial strategies for generations. The revival of this century-old therapy exemplifies how returning to nature can help address contemporary medical crises and promote more sustainable infection-control practices.

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CONFLICT OF INTEREST

The author declares no conflicts of interest, financial or otherwise, that could compromise the integrity, objectivity, or validity of the opinion or viewpoint expressed.

GRANT SUPPORT AND FINANCIAL DISCLOSURE

Authors declared no specific grant for this research from any funding agency in the public, commercial or non-profit sectors

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