



ОБЗОРЫ

REVIEW

DOI: <https://doi.org/10.36233/0507-4088-366>

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Viruses That Heal: Harnessing Bacteriophages in the Era of Antibiotic Resistance

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Abstract

The global rise in antimicrobial resistance (AMR) poses an urgent threat to public health, and novel alternatives to traditional antibiotics are needed. One of the most promising options is bacteriophages, viruses that infect and destroy bacteria. Once overshadowed by the discovery of antibiotics, phage therapy is now regaining attention, driven by advances in genomics, synthetic biology, and targeted medicine. This review examines the biology, diversity, and therapeutic use of bacteriophages in treating bacterial infections, especially those caused by multi-drug-resistant pathogens. It also discusses how phages act through natural mechanisms, such as lytic enzymes (holins, endolysins, and muralysins), and highlights new genetic engineering techniques, such as CRISPR-Cas systems, phage recombineering, and synthetic genome reboots. In addition to clinical applications, we evaluate phages as biocontrol agents for food safety, environmental sanitation, and biofilm management. Additionally, the article explores key issues in phage therapy, including regulatory frameworks, formulation stability, dynamics of phage-host resistance, and the importance of rapid diagnosis. When properly integrated into modern health and biotechnology practices, bacteriophages offer significant potential and a sustainable solution to the global challenge of antimicrobial resistance.

Keywords: *bacteriophage; phage therapy; antibiotic resistance; genetic engineering; infection control*

For citation: Awotundun Th.A., Samson O.J., Olanbiwoninu A.A. Viruses That Heal: Harnessing Bacteriophages in the Era of Antibiotic Resistance. *Problems of Virology (Voprosy Virusologii)*. 2026; 71(2): 91–108.

DOI: <https://doi.org/10.36233/0507-4088-366> EDN: <https://elibrary.ru/hoolym>

Acknowledgement. We sincerely express our appreciation to all the authors whose works were used for the writing of this review.

Conflict of interest. The authors declare no apparent or potential conflicts of interest related to the publication of this article.

ОБЗОР

DOI: <https://doi.org/10.36233/0507-4088-366>

Лечебные вирусы: использование бактериофагов в эпоху антибиотикорезистентности

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Резюме

Глобальный рост антимикробной резистентности (AMP) представляет собой серьезную угрозу для здоровья населения, в связи с чем возникает острая необходимость в новых альтернативах традиционным антибиотикам. Одним из наиболее перспективных вариантов являются бактериофаги – вирусы, которые поражают и уничтожают бактерии. Фаготерапия, некогда отошедшая на второй план после открытия антибиотиков, в настоящее время вновь привлекает к себе внимание благодаря достижениям в области геномики, синтетической биологии и персонализированной медицины. В данном обзоре рассматриваются биология, разнообразие и терапевтическое применение бактериофагов при лечении бактериальных инфекций, осо-

бенно вызванных патогенами с множественной лекарственной устойчивостью. В обзоре также обсуждаются естественные механизмы действия фагов, такие как литические ферменты (холины, эндолизины и мурализины), и подчеркиваются новые методы генной инженерии – CRISPR-Cas, рекомбинирование фагов и перезагрузка синтетического генома. Помимо клинического применения, фаги оцениваются как средства биологического контроля для обеспечения безопасности пищевых продуктов, санитарного состояния окружающей среды и борьбы с биопленками. Кроме того, в статье исследуются ключевые вопросы фаготерапии, включая нормативную базу, стабильность препаратов, динамику резистентности фагов и хозяев, а также важность быстрой диагностики. При правильном внедрении в современную практику здравоохранения и биотехнологии бактериофаги обладают значительным потенциалом и представляют собой устойчивое решение глобальной проблемы антимикробной резистентности.

Ключевые слова: бактериофаг; фаговая терапия; антимикробная резистентность; генная инженерия; профилактика инфекций

Для цитирования: Авотундун Т.А., Сэмсон О.Д., Оланбивонину А.А. Лечебные вирусы: использование бактериофагов в эпоху антибиотикорезистентности. *Вопросы вирусологии*. 2026; 71(2): 91–108.

DOI: <https://doi.org/10.36233/0507-4088-366> EDN: <https://elibrary.ru/hoolum>

Благодарности. Мы искренне благодарим всех авторов, работы которых были использованы при написании данного обзора.

Конфликт интересов. Авторы подтверждают отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

1. Introduction

The microbial world is vast, diverse, and intricately connected through ecological and evolutionary interactions. Microorganisms, including bacteria, archaea, viruses, fungi, protozoa, algae, and helminths, are foundational to ecosystem stability and human health [1, 2]. Among microbial interactions, bacteria and viruses (bacteriophages) maintain dynamic evolutionary relationships that include both antagonistic infection cycles and beneficial population-level effects, shaping microbial community structure and ecosystem processes [3].

In recent decades, the global surge in antibiotic resistance has emerged as a critical public health threat, prompting urgent calls for alternative antimicrobial strategies [4–7]. The overuse and misuse of antibiotics in medicine, agriculture, and animal husbandry have accelerated the emergence of multidrug-resistant (MDR) bacterial strains, rendering many conventional treatments ineffective [8–13]. In response to this growing crisis, interest has been revitalized in a long-underexplored antibacterial strategy; bacteriophages, or phages: viruses that specifically infect and lyse bacteria [14–17].

First discovered over a century ago, bacteriophages are the most abundant biological entities on Earth, with an estimated 10^{31} particles globally [18]. Their remarkable specificity, self-amplifying nature, and ability to disrupt bacterial biofilms offer several advantages over traditional antibiotics. Unlike broad-spectrum antimicrobials, phages can be engineered or selected for targeted precision therapy, reducing collateral damage to the host microbiota [19]. Advances in synthetic biology, genetic recombineering, and CRISPR-Cas systems have further propelled phage research into the realms of personalised medicine, biotechnology, and environmental biocontrol [20].

This review presents a comprehensive synthesis of the ecological roles and molecular mechanisms of bacteriophages in controlling bacterial infections, particularly within the context of antibiotic resistance. We discuss natural and engineered phage strategies, including lytic

proteins (holins, endolysins, murins), genome engineering approaches, and the prospects of phage therapy in clinical and industrial settings. Furthermore, we explore the regulatory, technical, and biological challenges that must be overcome to harness phages as next-generation antimicrobials fully.

As the world stands on the precipice of a post-antibiotic era, bacteriophages are re-emerging as powerful allies in our fight against resistant pathogens. Their integration into modern medicine and biotechnology could redefine the future of infection control and global health.

2. Microbial Diversity, Distribution and Interactions

Microorganisms form the unseen foundation of Earth's biosphere, playing vital roles in nutrient cycling, ecosystem stability, and human health [21]. They are evolutionarily diverse, metabolically versatile, ubiquitous and exist in every conceivable habitat, from deep-sea hydrothermal vents to the human gut [22]. The major microbial groups include bacteria, viruses, archaea, fungi, protozoa, and algae, each with distinct structural, genetic, and ecological attributes.

Bacteria are prokaryotic, unicellular organisms that inhabit virtually all environments. They can be autotrophic or heterotrophic, aerobic or anaerobic, and display a wide range of morphologies and metabolic pathways [23]. Viruses, on the other hand, are acellular entities composed of genetic material encased in a protein coat, requiring host cells: bacterial, archaeal, or eukaryotic, for replication [3]. Archaea, though also prokaryotic, differ significantly from bacteria in their membrane lipids, genetic machinery, and extremophile lifestyles [24, 25].

Fungi are eukaryotic organisms that range from unicellular yeasts to complex multicellular molds and mushrooms. They play essential roles in decomposition, symbiosis, and disease [26]. Protozoa are single-celled eukaryotes, often motile, and can be free-living or parasitic [27]. Algae, a polyphyletic group of photosynthetic eukaryotes, range from microscopic phytoplankton to large seaweeds and serve as primary producers in aquatic ecosystems [28].

Despite their diversity, microorganisms rarely exist in isolation. They engage in complex interactions, including mutualism, commensalism, parasitism, amensalism, competition, and predation, that shape their survival and ecological impact [29]. These interactions are not static; environmental conditions, nutrient availability, and the presence of other species influence them. For instance, mutualistic interactions such as syntrophic relationships between hydrogen-producing bacteria and methanogenic archaea are essential in anaerobic digestion [30]. Conversely, antagonistic interactions, such as the production of bacteriocins or phage-mediated lysis, help regulate microbial populations and can be exploited for therapeutic purposes [31].

A particularly intriguing interaction is the one between bacteria and fungi. These two dominant microbial groups co-occur in diverse niches, including soil, plant surfaces, and the human microbiome [2]. Bacterial-fungal interactions (BFIs) can range from cooperative (e.g., nutrient sharing, biofilm co-formation) to antagonistic (e.g., production of antibiotics, lytic enzymes, or reactive oxygen species). These interactions have profound implications in agriculture, biotechnology, and medicine (Fig. 1). For example, fungal pathogens may be suppressed by bacterial antagonists in the rhizosphere, whereas certain bacteria may exploit fungal hyphae for spatial expansion, a phenomenon termed the “fungal highway” [32, 33]. In clinical settings, BFIs can influence disease progression and treatment outcomes; their co-existence in polymicrobial biofilms results in enhanced virulence and increased resistance to antimicrobials [34], as seen in polymicrobial infections involving *Candida albicans* and *Staphylococcus aureus* [2].

3. Bacteriophage–Bacteria Interactions

Viruses are the most abundant biological entities on Earth, with an estimated 10^{31} particles populating diverse environments, from oceanic waters to animal guts [35]. These acellular agents consist of genetic

material, either DNA or RNA, encapsulated within a protein shell known as the capsid, and in some cases, surrounded by a lipid envelope. Viral genomes can be single- or double-stranded, linear or circular, and encode the minimal information required for hijacking a host’s cellular machinery to propagate [36].

Among viruses, bacteriophages (phages) occupy a unique as viruses that infect bacteria and profoundly influence bacterial population dynamics, evolution, and gene exchange. These viruses specifically infect bacterial cells and play a critical role in regulating bacterial populations in virtually all ecosystems [14]. Structurally, bacteriophages exhibit considerable diversity, including tailed double-stranded DNA viruses classified within the class *Caudoviricetes* (e.g., families *Autographiviridae*, *Demereviridae*, *Drexlerviridae*, *Chaseviridae* and *Herelleviridae*, among others), as well as filamentous phages such as those in the family *Inoviridae* and pleomorphic forms such as *Plasmaviridae* [37, 38]. Tailed bacteriophages represent the majority of currently described phages and are considered among the most abundant biological entities on Earth. Most characterized phages possess double-stranded DNA genomes, although single-stranded DNA and RNA phages have also been described [39].

3.1. Biology and Mechanism of Action of Bacteriophage

Bacteriophages infect specific bacterial hosts and, in the lytic cycle, hijack the bacterial cellular machinery to replicate, ultimately lysing the host cell and releasing progeny virions.

3.1.1. Life Cycles of Bacteriophages

Phages employ different strategies to replicate within their bacterial hosts, primarily through lytic, lysogenic, or chronic infection cycles (Fig. 2):

- **Lytic Cycle:** In this virulent replication strategy, the phage attaches to the host cell, injects its genome, and hijacks the bacterial machinery to produce viral compo-

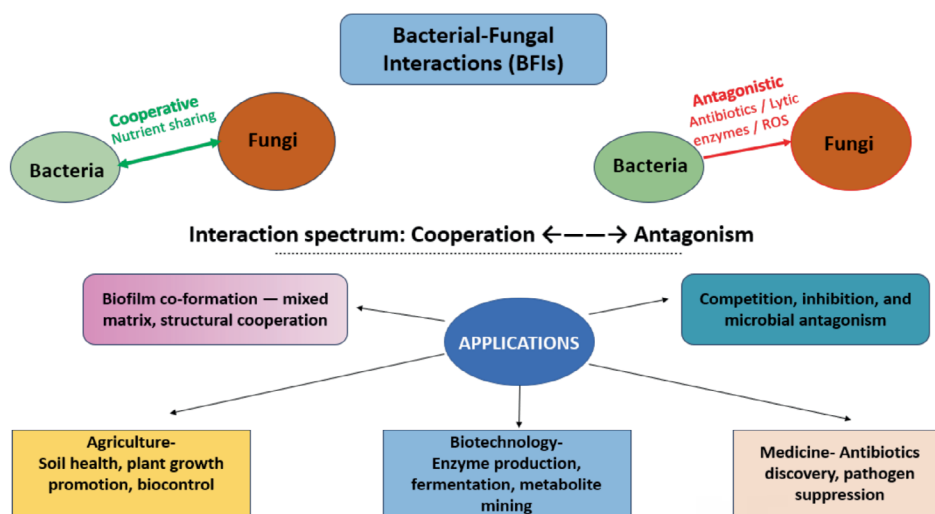


Fig. 1. Bacterial-Fungal Interactions and Their Applications.

Рис. 1. Взаимодействия между бактериями и грибами и их применение.

nents. These assemble into mature virions, which are then released through the lysis of the host cell. Phages that exclusively replicate via this pathway are termed virulent (lytic) phages. Virulent phages, such as T4, are ideal candidates for phage therapy due to their rapid bactericidal action [40, 41].

- **Lysogenic Cycle:** In temperate phages (e.g., λ phage), the viral genome integrates into the bacterial chromosome as a prophage and replicates passively with the host genome. Environmental stressors can induce the prophage to excise and enter the lytic cycle. This strategy enables long-term persistence and facilitates horizontal gene transfer but may contribute to lysogenic conversion, a process in which bacterial hosts acquire virulence or antibiotic resistance genes, raising concerns for therapeutic applications [40].

- **Chronic Cycle:** Some filamentous phages (e.g., M13) adopt a chronic infection strategy, continuously releasing new virions without lysing the host. These phages establish a long-term presence, influencing host physiology and gene expression [42].

3.2. Host Specificity and Receptor Recognition

Phages display a high degree of host specificity. They are usually species- or even strain-specific, despite their affinity for living cells, which is the case for the bacterial hosts they infect, i.e., they infect only a specific species or strain within several bacterial species. This specificity is determined by the interaction between the phage's adsorption structures, such as tail fibres, spikes, or base plates, and receptors on the bacterial surface. These receptors may include outer membrane proteins (e.g., OmpC, OmpA), Lipopolysaccharides (LPS), Teichoic acids, Pili, and flagella [31]. Phages first produce the lytic cycle where the attachment of the phage to the bacterial host occurs, the phage then injects its genome into the bacterial host cell, reproduces by taking hold of the host's molecular machinery, and finally lyses the bacterial host cell, at the same time releasing its progeny [20].

The specificity of bacteriophage infection has enhanced their application in various fields, including health, biotechnology, ecology, and environment (bacterial control), and as environmental monitoring agents [43–46]. The specificity of the bacteriophage is due to an affinity for specific receptors, as shown in **Table 1** below.

4. Lytic Enzymes: Holins, Endolysins, and Murins

Successful lysis of the bacterial host in the lytic cycle involves a coordinated action of phage-encoded enzymes:

- **Holins:** The holins are small membrane proteins employed in the host cell for the perforation of the host bacterial cytoplasmic membrane at a precisely timed moment during infection. They work in synergy with the endolysins by giving them access to the bacterial host peptidoglycan, which is then followed by the destruction of the bacterial cell wall [65].

- **Endolysins:** These are peptidoglycan-degrading enzymes that cleave specific bonds in the bacterial cell wall. Their structure and activity vary based on target: Gram-positive endolysins often contain modular domains for binding and catalysis, while Gram-negative phage endolysins typically require holins for entry [31, 66]. Endolysins perform the activities of some enzymes, such as lytic transglycosylase, glycosidase, amidase, or endopeptidase, to destroy bacterial cells by murein destruction. The release of progeny virions is aided by endolysins [65].

- **Murins:** Also known as spanins or auxiliary lytic enzymes, these proteins disrupt outer membrane components in Gram-negative bacteria, completing the lysis process initiated by holins and endolysins [65].

The synergy of these lytic proteins ensures efficient bacterial cell rupture and rapid release of progeny virions. Engineered versions of these enzymes, such as artilysins, are currently being explored as novel antimicrobials independent of whole phage particles [67]. Together, the structural precision, host specificity, and powerful lytic

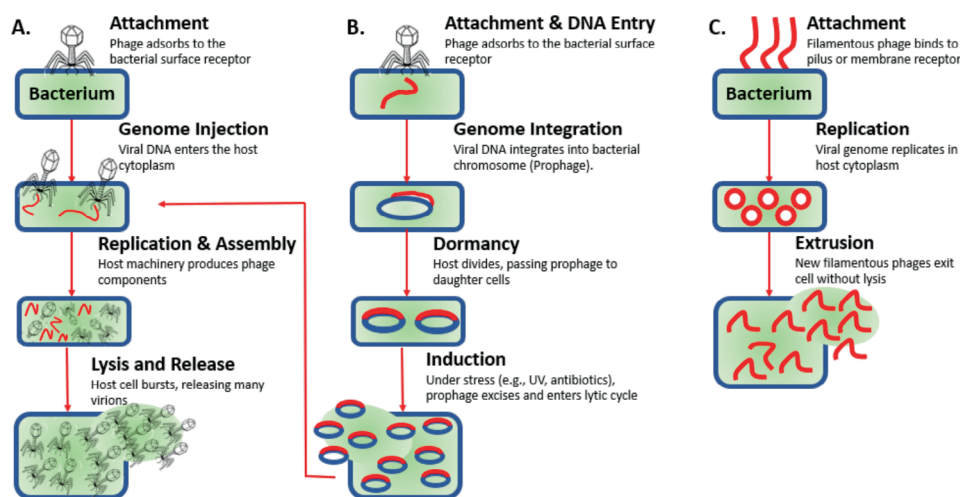


Fig. 2. Life cycles of bacteriophages: lytic cycle (a); lysogenic cycle (b); chronic cycle (c).

Рис. 2. Жизненные циклы бактериофагов: литический цикл (a); лизогенный цикл (b); хронический цикл (c).

Table 1. Characterized bacteriophages, their bacterial hosts, and associated host cell receptors

Таблица 1. Характеристика бактериофагов, их бактериальных хозяев и связанных с ними рецепторов клеток-хозяев

Phage	Bacterial host	Receptor	References
Sf6	<i>Shigella flexneri</i>	OmpA OmpC	Parent et al. (2014) [47]
SfMu	<i>Shigella flexneri</i>	O-antigen of lipopolysaccharides	Jakhetia & Verma (2015) [48]
KSF-1	<i>Vibrio cholera</i>	Mannose-sensitive haemagglutinin type IV pilus	Faruque et al. (2005); Das et al. (2013); Pattnaik et al. (2023) [49–51]
ICP1	<i>Vibrio cholera</i>	O1 antigen	Seed et al., 2012 [52]
PPO1	<i>Escherichia coli</i>	OmpC	Morita et al., 2002 [53]
φiV10	<i>Escherichia coli</i>	O157 antigen	Perry et al., 2009 [54]
9NA	<i>Salmonella typhimurium</i>	O-antigen of LPS	Schmidt et al., 2016 [55]
F336	<i>Campylobacter jejuni</i>	O-methyl phosphoramidate (MeOPN)	Sørensen et al., 2011 [56]
F341	<i>Campylobacter jejuni</i>	Flagellum	Baldvinsson et al., 2014 [57]
JG004	<i>Pseudomonas aeruginosa</i>	O-antigen of LPS	Le et al., 2013 [58]
Phage K8	<i>Pseudomonas aeruginosa</i>	O-antigen of LPS	Pan et al., 2016 [59]
Gamma phage	<i>Bacillus anthracis</i>	GamR (LPXTG-harboring protein) CsaB	Gillis et al., 2014 [60]
AP50c	<i>Bacillus anthracis</i>	CsaB	Bishop-Lilly et al., 2012 [61]
φi11	<i>Staphylococcus aureus</i>	wall teichoic acids (WTA)	Xia et al., 2011 [62]
ΦiSLT	<i>Staphylococcus aureus</i>	Lipoteichoic acids (LPA)	Kaneko et al., 2009 [63]
A118	<i>Listeria monocytogenes</i>	Rhamnose residues in WTA	Bielmann et al., 2015 [64]
P35	<i>Listeria monocytogenes</i>	Rhamnose and N-acetylglucosamine	Bielmann et al., 2015 [64]

arsenal of bacteriophages provide a strong foundation for their deployment in modern microbial control strategies.

There are three types of holins, classified as I, II, and III, which differ based on the sequences of their amino acids; however, these differences do not affect their functions [68]. Holins are membrane proteins that typically contain one or more hydrophobic transmembrane domains and a C-terminal region with charged residues that may influence their membrane topology and function. Class I holins have proteins with more than 95 residues of amino acid with three hydrophobic transmembrane helices. Class II holins have two hydrophobic transmembrane helices with 65–95 amino acid residues; however, class III holins have only one hydrophobic transmembrane helix [65].

5. Genetic Engineering of Bacteriophages

The genetic manipulation of bacteriophages has evolved from early foundational work into a sophisticated platform with vast applications in synthetic biology, medicine, diagnostics, and nanotechnology. With rising antimicrobial resistance and the limitations of traditional antibiotics, engineering phages for precision therapy has garnered renewed attention. Modern techniques now allow researchers to reprogram phage genomes for enhanced host specificity, lytic efficiency, payload delivery, and regulatory control [15, 69–71].

5.1. Historical Background of Phage Discovery and Early Applications

Bacteriophages were independently discovered early in the 20th century by Frederick Twort (1915) and Fé-

lix d’Hérelle (1917) [72, 73]. Shortly after their discovery, phages were explored as therapeutic agents to treat bacterial infections, especially in Eastern Europe and the former Soviet Union [71, 74, 75]. However, enthusiasm for phage therapy waned in the West with the advent of antibiotics in the 1940s, which at the time were proven to have greater potency [70, 76–78].

Despite this, phages remained crucial tools in molecular biology. Phage applications have greatly expanded as a result of recent breakthroughs, particularly in genome engineering. Phages have been employed in synthetic biology, material science, and biomedical sectors in addition to antibacterial therapy. Given their abundance and diversity, phage engineering for many applications has a lot of potential [79, 80]. Random mutagenesis was the sole way to make genetic changes until the late 1970s. Subsequently, recombinant DNA technology enabled researchers to genetically modify bacteriophages, including early gene manipulation studies using phage T4. Since then, targeted mutagenesis approaches have been improved regularly [69, 81]. Some of the strategies popular in phage genome engineering are further discussed as follows.

5.2. Rebooting Phages from Synthetic Genomes

Phages can be rebooted utilizing assembled phage genomic DNA by transforming the host’s phage genomic DNA, which already has the requisite mutations. The infectious phages will be assembled following the replication, transcription, and translation of the genomic DNA in the hosts’ cells [82]. Polymerase cycling assembly (PCA) is employed to assemble the genomic DNA of phages that have small to

medium DNA molecules, as seen in phiX174 with 5,386 bp, using synthetic oligonucleotides that will span the entire genome with overlap sequences. On the contrary, ligation of individual genomes, hitherto clipped by restriction enzymes, is the case in much larger DNA molecules, for example, T7 with 39, 937 bp [83, 84]. They can also be pieced together using transformation-associated recombination (TAR) from overlapping smaller pieces. The genomic DNA so assembled can be reactivated when introduced into suitable hosts, or through the use of potentially suitable cell-free systems in phage genome ‘rebooting’. As a result, the phages have been multiplied on the appropriate strain and isolated from rebooting responses [85].

Transformation-associated recombination uses a significant level of homologous recombination and is capable of assembling DNA up to 300 kb in length. This has been observed in yeast-based genome assembly and rebooting in *Escherichia coli*. Polymerase chain reaction (PCR) was employed to amplify the overlapping fragments from the genome, with each adjacent fragment having a homologous sequence. The fragments were then recombined in a yeast vector to generate a complete phage genome. It is plausible to introduce desired mutations into the fragments to generate any desired phage mutants. The DNA of the engineered yeast cell was then extracted and transformed into host cells to generate synthetic phages [86, 87].

5.3. Bacteriophage Recombineering of Electroporated DNA (BRED)

BRED is a targeted mutagenesis approach used primarily in lytic mycobacteriophages, enabling precise genetic alterations without the need for selectable markers [87, 88]. It employs recombineering proteins (e.g., RecE/RecT or Che9c gp60/gp61) expressed in a recombination-proficient bacterial host [88, 89].

In BRED, the phage genomic DNA and the donor DNA (bearing the desired mutation) are co-electroporated into the host cell. Homologous recombination occurs during phage replication, and progeny phages with the engineered mutation can be isolated by PCR screening [90]. This method has successfully produced deletions, insertions, and point mutations in various phages, including those infecting *Mycobacterium smegmatis* [89], *Salmonella* [91, 92], *Escherichia coli* [93, 94] and *Klebsiella* [95].

5.4. CRISPR-Cas Systems for Phage Genome Editing

The Clustered regularly interspaced short palindromic repeats (CRISPR) in combination with *cas* (CRISPR-associated) genes (CRISPR-Cas system), initially characterized as a bacterial adaptive immune mechanism, has revolutionized phage genome editing. The CRISPR-Cas systems consist of two main components: the Cas proteins, which work as the catalytic core of the system and are responsible for cleaving DNA, and the CRISPR locus, which functions as the genetic memory that directs catalytic activity against foreign DNA [96]. In this context, CRISPR-Cas can be used in two major ways:

Selective pressure and counter-selection: CRISPR-Cas can be programmed to target the wild-type phage genome, allowing only recombinant phages with desired

mutations to escape cleavage and propagate [81, 97, 98].

Precise editing: Cas9 or Cas12 proteins directed by guide RNAs can introduce double-stranded breaks at specific genomic loci. This is followed by homology-directed repair using donor DNA, enabling insertion, deletion, or substitution of genes [99].

Phage editing using CRISPR has been demonstrated in T7 [100], *Listeria* [101], *Vibrio cholerae* [98], and *Staphylococcus* phages [97, 102]. Notably, it has enabled the deletion of virulence genes, reprogramming of host range, and introduction of synthetic circuits.

6. Clinical and Industrial Applications of Bacteriophages

Bacteriophages are increasingly recognized as valuable tools across clinical, agricultural, food safety, and environmental sectors (Fig. 3). Their host specificity, self-replicating nature, and adaptability offer unique advantages over conventional antimicrobials.

6.1. Phage Therapy

6.1.1. Treating MDR Infections in Humans and Animals

Interestingly, the emergence of antibiotic-resistant bacteria and even rise in the multi-antibiotic-resistant bacterial infections, as well as the limited rate of new antibiotic discoveries, has heightened the need for phage-based therapeutics [103, 104]. Bacteriophages can infect and destroy antibiotic-resistant bacteria even without any known negative consequence on the cells of their living hosts like humans, animals and plants [105]. They could be used alone or together with antibiotics to treat bacterial infections [104]. This phenomenon is known as Phage Therapy or Bacteriophage Therapy.

Phages have demonstrated efficacy against a wide range of clinically relevant bacteria, including *Acinetobacter baumannii* [106], *Pseudomonas aeruginosa* [107], *Escherichia coli* [108], *Staphylococcus aureus* [109], and *Klebsiella pneumoniae* [110]. Animal studies have shown success in preventing or treating infections such as osteomyelitis [111, 112], skin wounds [113], respiratory tract infections [106].

6.1.2. Phage-Antibiotic Synergy

Combining phages with antibiotics can yield synergistic effects, where phage-induced lysis enhances antibiotic penetration and biofilm disruption [114–116]. This phage-antibiotic synergy (PAS) can improve therapeutic efficacy and reduce the required dosage of antibiotics, potentially slowing resistance development [117]. PAS has shown promise in both *in vitro* studies [115, 116, 118] and *in vivo* models [119, 120], particularly against biofilm-associated and other difficult-to-treat infections.

6.1.3. Case Studies and Clinical Trials

Clinical trials evaluating phage safety, efficacy, and pharmacokinetics are steadily increasing. Trials have targeted infections such as diabetic foot ulcers, urinary tract infections, septicemia, cystic fibrosis-related lung infections, and otitis externa, among others [121]. Several

studies report favourable outcomes, with good tolerability and minimal side effects.

Compassionate-use cases have illustrated the power of phages to reverse life-threatening, antibiotic-resistant infections. Schooley *et al.* (2017) [122] reported an incident in San Diego, where a patient was infected with a multidrug-resistant *Acinetobacter baumannii* strain on a trip to Egypt. The patient fell into a coma for over two months, but awoke two days later after receiving an intravenous injection of a phage mixture that killed the bacteria and eventually recovered completely. Law *et al.* (2019) [123] also reported that the use of intravenous bacteriophage therapy (BT) along with systemic antibiotics in a 26-year-old cystic fibrosis patient awaiting lung transplantation resulted in non-recurrence of pseudomonal pneumonia and cystic fibrosis exacerbation within 100 days following the end of PAS therapy. The patient underwent successful bilateral lung transplantation 9 months later. These events reignited global interest in phage-based treatments. Other clinical studies on phage therapy are summarized in **Table 2**.

However, widespread clinical integration awaits rigorous, large-scale randomised trials and clear regulations to standardise phage production, purification, and administration [124].

6.2. Biocontrol in Agriculture and Food Industry

Phages are also widely explored in agriculture and the food industry to reduce reliance on the use of antibiotics in animal husbandry, and control of pathogens in food

6.2.1. Application of Phages in Animal Husbandry

The abuse of antibiotics in livestock farming has contributed to the acceleration of antibiotic resistance, as bacteria in animals can become resistant, which may then be transferred to humans through the food chain. Phages offer a promising alternative for controlling bacterial infections in livestock, thereby improving their health, decreasing antibiotic usage and ultimately leading to the production of safer food products [121, 125]. Several studies have reported the effective use of phages to target and eliminate bacterial pathogens in livestock. Such studies include the reduction and control of *Salmonella enterica* serovar Enteritidis colonisation in poultry [126], treatment of bovine mastitis *Staphylococcus aureus* using lytic bacteriophage [127–129], and reduction in the mortality rate of Rainbow trout fish (*Oncorhynchus mykiss*) caused by pathogenic *Aeromonas hydrophila* infection [130], among others.

6.2.2. Controlling Foodborne Pathogens

Foodborne bacterial infections caused by *Salmonella* spp., *Listeria monocytogenes*, *Campylobacter jejuni*, *Clostridium* spp., *Staphylococcus aureus* and pathogenic *E. coli* strains are of global public health concern. Bacteriophages offer a natural, residue-free, and highly specific method to reduce bacterial contamination on raw meat, dairy products, fresh produce, ready-to-eat foods and food packaging [131, 132].

Phages can be applied by spraying, dipping, or coating and are effective in both pre-harvest and post-harvest.

They can reduce pathogen load without altering food sensory qualities or nutritional content, making them an ideal food safety intervention [133–135].

Currently, several commercial phage-based products have been certified and approved by the United States Department of Agriculture (USDA) for the biocontrol of pathogenic bacteria. Examples include:

- ListShield – a phage cocktail formulation targeting *Listeria monocytogenes* usually used in fresh produce, dairy products, fish, and ready-to-eat foods [136].
- EcoShield – a phage designed to control *E. coli* O157:H7 in beef [137].
- SalmoFresh – a cocktail containing six different phages, effective against *Salmonella* spp. It is capable of killing the most common serotypes such as Typhimurium, Enteritidis, Heidelberg, Newport, Hadar, Kentucky, Thompson, Georgia, Agona, Grampian, Senftenberg, Alachua, Children's, Reading, and Schwarzengrund [138, 139].
- Listex – a P100 phage suspension formulation, effective against *Listeria monocytogenes*. It is used in meat, fish, seafood, dairy products, and other ready-to-eat foods, in a concentration of up to 1×10^9 Plaque-Forming Units (PFU) per cm^2 [140].

6.3. Environmental and Surface Decontamination

6.3.1. Application in Waste Treatment and Surface Cleaning

Phages are being increasingly explored for their role as cleaning agents in environmental sanitation and hospital hygiene. On surfaces, phage-based cleaners have been shown to effectively disinfect areas contaminated with *Staphylococcus aureus*, *P. aeruginosa*, and *Salmonella*. These biological disinfectants offer a safer alternative to harsh chemical agents and can be used in healthcare settings, restaurants, food processing facilities, and even on medical devices [141, 142]. In wastewater treatment plants, phages can be used to reduce harmful bacterial populations and biofilms, improving effluent quality and safety [143–145].

6.3.2. Ecological Significance in the Environment

In soil as well as in other environments, phages can mediate bacterial growth rates and selectively impact the diversity of bacterial communities. They play unique roles in different environments [19].

7. Phage Therapy Prevailing Over Antibiotics

Phage therapy offers several advantages over antibiotics. These include their specificity, adaptability, safety, and efficacy against biofilms and resistant strains (**Fig. 4**). In the face of increasing antimicrobial resistance and a stagnant antibiotic development pipeline, bacteriophages represent an effective, nature-derived, and evolution-directed alternative for modern antimicrobial therapy.

7.1. Target Specificity and Preservation of Microbiota

Conventional antibiotics often act on broad bacterial targets, eliminating not only the pathogenic strains but al-

so beneficial commensals that support digestion, nutrient absorption, and immune modulation [160]. This dysbiosis is associated with side effects such as gastrointestinal distress, opportunistic infections, and weakened host defences. In contrast, phages demonstrate highly specific activity, infecting only the bacterial strain they are adapted to target, thereby preserving the natural microbiota and reducing both unintended side effects and the likelihood of resistance development [161].

7.2. Reduced Potential for Inducing Resistance

The emergence of “superbugs”, bacteria resistant to multiple classes of antibiotics, is a major concern in public health. Bacterial resistance mechanisms include enzymatic degradation, target site modification, and efflux pumps [162]. Phages, however, utilise entirely different mechanisms of action and are less prone to inducing resistance. Even if resistance occurs, phages can be rapidly upgraded or used in cocktails to maintain efficacy. Their co-evolutionary nature has an adaptive advantage over static chemical drugs [163, 164].

7.3. Low Inherent Toxicity

Phages consist of nucleic acids and proteins, which render them intrinsically nontoxic to eukaryotic cells [165]. Unlike certain antibiotics, which are characterised by nephrotoxicity or hepatotoxicity, phages are harmless at the physiological level [166]. Although immune responses may occur after phage administration systemically, instances of adverse effects are infrequent

and comprise mild and reversible physiological and immunological effects [167].

7.4. Speeded-Up Discovery and Isolation

Phages may be rapidly isolated from high-microbial diversity environments, e.g., sewage, soil, or wastewater, with specific bacterial strains serving as hosts [168]. Phage discovery is thus faster and less expensive than the optimisation, screening, and toxicity testing required for antibiotic development over the years. Isolation of phages against fastidious or non-culturable bacteria is sometimes challenging [169], but otherwise, the process is faster and less expensive than traditional antibiotic pipelines.

7.5. Lack of Cross-Resistance to Antibiotics

Phages and antibiotics act through distinct mechanisms; resistance to one antibiotic will not confer resistance to another. Phages are thus a great option for treating infections resistant to antibiotics, such as methicillin-resistant *Staphylococcus aureus* (MRSA) and carbapenem-resistant Enterobacteriaceae [170]. They may also be co-administered with antibiotics for enhanced activity by synergistic means.

7.6. Versatile Formulation and Administration Routes

Like antibiotics, phages can be formulated into various delivery forms, including liquids, powders [171–173], creams [174], sprays [175], encapsulated tablets [176], and even phage-impregnated materials [177]. They are also suitable for various administration routes; oral, topi-

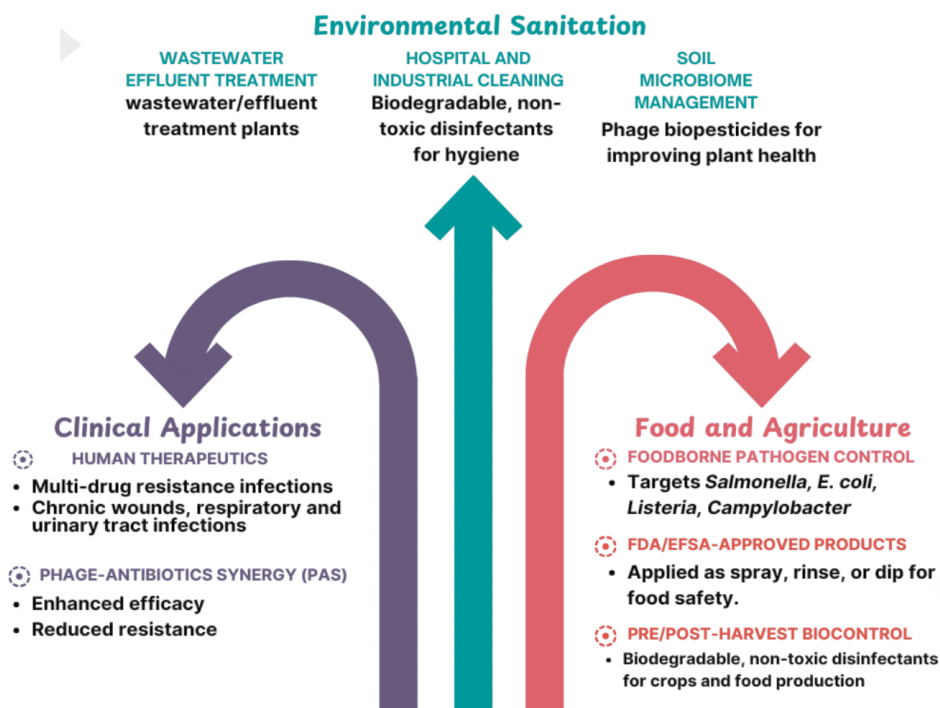


Fig. 3. Clinical and industrial applications of bacteriophage.

Рис. 3. Клиническое и промышленное применение бактериофагов.

Table 2. Clinical application of bacteriophages in some selected studies carried out on animals and humans to treat bacterial infection

Таблица 2. Клиническое применение бактериофагов в ряде отдельных исследований, проведенных на животных и людях с целью лечения бактериальных инфекций

Infection	Causative agent	Bacteriophage used	Dose and route of administration	Study model	Study outcome	References
Studies in animals						
Pneumonia	Carbapenem-resistant <i>Acinetobacter baumannii</i>	YMC 13/03/R2096 ABA BP (phage Bφ-R2096)	Single phage dose; Intranasal	Mice	Increased the survival rates of mice from 30% with MOI=0.1 to 100% with MOI=10 for 12 days. Ameliorated histologic damage to infected lungs, with bacterial clearance in the lungs observed on day 3 post-infection. No mortality or serious side effects in phage-treated groups	Jeon et al., 2019 [146]
Pneumonia, septicemia and urinary tract infection	<i>E. coli</i> ST131-O25b:H4	LM33_P1	0.3, 3, or 10 (1.2×10^7 , 1.2×10^8 or 4×10^9 PFU); Intranasal and intraperitoneal	Mice	Reduce the bacterial load in several organs, including the heart, lungs, liver, spleen and kidneys	Dufour et al., 2016 [147]
Skin infection	<i>Pseudomonas aeruginosa</i>	PlyPa03	Single 300-μg dose	Mice	> 2log mean reduction in bacterial load	Raz et al., 2019 [148]
Lung infection	<i>P. aeruginosa</i>	PlyPa91	50 μL of 1.8-mg/ml; Intranasal/ Intratracheal	Mice	20% survival for IN administration, 70% survival for IT administration (10-day period)	Raz et al., 2019 [148]
Lobar Pneumonia	<i>Klebsiella pneumoniae</i>	vB_KpnM-Teh.1	10^{10} PFU; Intraperitoneal 10^{10} БОЕ	Mice	Resulted in 7 log ₁₀ reduction, no lung enlargement or abscesses	Sasani & Eftekhari, 2020 [149]
Bacteremia	<i>A. baumannii</i>	NA	0.3 mL of 10^8 PFU/mL of a therapeutic phage; Intraperitoneal	Mice	Treated mice stayed alive for more than 6 weeks, with full physical activity	Jasim et al., 2018 [150]
Bacteremia	<i>K. pneumoniae</i>	Dp42	Prophylactic treatment: 50 μg/mouse; Intraperitoneal, single dose 6h before infection. Therapeutic treatment: 50 μg/mouse; Intraperitoneal, single dose 30 min after infection	Mice	100% survival in both prophylactic and therapeutic treatment. Bacterial load in the mouse organs (liver, spleen and lungs) were significantly reduced	Wang et al., 2019 [151]
Bacteremia	<i>P. aeruginosa</i>	RLP	10^9 PFU/mouse; Intraperitoneal, single dose	Mice	92% survival rate in the treated group compared with 7.4% in the untreated group	Alvi et al., 2020 [152]
Bacteremia	Multidrug-Resistant Gram-Negative <i>A. baumannii</i>	PlyF307	1 mg of lysin, transcathe-ter, 2 doses, 4 hours apart	Mice	2log ₁₀ reduction in catheter-mimicking model, with phage administration 24 hpi in bacteremic mice. 50% survival in treated mice	Lood et al., 2015 [153]
Wound infection	<i>A. baumannii</i>	Phage mixture (AbArmy φ1, AbNavy φ1, AbNavy φ2, AbNavy φ3, and AbNavy φ4)	10^8 PFU/mouse; Intraperitoneal, and 5×10^7 PFU topically in Tegaderm dressing, at 4h, 24h, and 48h post-infection	Mice	Effectively decreased wound size of mice infected without adverse effects	Rouse et al., 2020 [154]
Gastrointestinal infection	<i>E. coli</i>	T4	3.6×10^7 PFU; Transdermal or orally	Rat	83.33% survival rate in the formulation-treated group	Rastogi et al., 2017 [155]

For continuation of Table 2, see page 100.

REVIEWS

Infection	Causative agent	Bacteriophage used	Dose and route of administration	Study model	Study outcome	References
Fracture-related infection of the tibia (tibial osteotomy with plate fixation)	Methicillin-resistant <i>Staphylococcus aureus</i>	ISP	10 ⁹ PFU/mL; intravenously and locally	Sheep	Phage neutralisation levels reached a maximum of 99.9% earlier, with no significant differences between intravenous and local administration. The bacterial load was not significantly changed, either intravenously or locally applied.	Peez et al., 2025 [156]
Studies in Humans						
Burn wound infection	<i>P. aeruginosa</i>	PP1131	10 ⁶ PFU; Topically, once daily for 7 days	Human	Bacterial burden in the most infected wound was reduced by two quadrants or more in half of the participants at the end of phage treatment. Few adverse events were reported	Jault et al., 2019 [157]
Pneumonia in Cystic Fibrosis (CF) patient	multidrug-resistant <i>P. aeruginosa</i>	AB-PA01	4 × 10 ⁹ PFU, Intravenously, every 6 hours, for 8 weeks	Human	The patient had no fever on day 7, and oxygen administration was reduced on day 8. The patient became ambulatory, was discharged from the hospital, and did not develop pneumonia during the 100-day follow-up period. No adverse events related to the phage were noted clinically or on laboratory monitoring (liver function tests, complete blood counts, electrolytes)	Law et al., 2019 [123]
Gallstone-induced acute pancreatitis with a pancreatic pseudocyst	<i>A. baumannii</i>	ΦPC ΦIV	4 × 10 ⁹ PFU ΦPC, initially through percutaneous catheters. After non-responsiveness, ΦIV was also administered for a total of 18 weeks	Human	The patient awoke from coma and became conversant. The patient's renal function (with an initial serum creatinine of 3.68 mg/dL) improved, and his general condition also improved gradually. He was discharged from the hospital on day 245 and resumed his normal life.	Schooley et al., 2017 [122]
UTI	<i>Staphylococcus aureus</i> , <i>E. coli</i> , <i>Streptococcus</i> spp., <i>P. aeruginosa</i> , <i>Proteus mirabilis</i>	NA	10 ⁷ –10 ⁹ PFU; Transurethral catheter, every 12h	Human	2–3log ₁₀ reduction in CFU or complete eradication of the pathogen in some patients	Ujmajuridze et al., 2018 [158]
Poly-microbial Bone (left tibia) Infection	Drug-resistant <i>A. baumannii</i> and multidrug-resistant <i>K. pneumoniae</i>	Combination of φAbKT21phi3 and φKpKT-21phi1	5 × 10 ⁷ PFU/ml; Intravenous	Human	Wound recovery started within few days of treatment and the wound eventually healed completely and patient's pain disappeared; 8 months post-treatment, the patient did not show any re-infection with either organism	Nir-Paz et al., 2019 [159]

cal, intravenous, intranasal, and even rectal, offering flexibility for diverse therapeutic practices.

7.7. Biofilm Disruption Capability

Bacterial biofilms are highly antibiotic-resistant due to their limited penetration and the presence of resting and persistent cells. Phages can disrupt biofilms through the enzymatic degradation of the extracellular polymeric substance (EPS) matrix by depolymerases or repeated lysis of the surface layer, enabling deeper penetration [178, 179].

Phages are thus excellent potential therapeutic agents for treating chronic and device-mediated infections.

7.8. Additional Benefits

Several secondary benefits include:

- Increased *in situ* replication results in single-dose potential.
- Lowers dosages required due to self-amplification.
- Single-hit kinetics, where the possibility of one bacterium being killed by one phage exists.

- Horizontal transfer among hosts takes place under specific conditions.
- Low ecological impact because the phages are biodegradable.
- The phages will not contribute to antibiotic resistance as non-antibiotic agents.
- Natural origin since the phages occur naturally in several different ecosystems.
- Cost-effectiveness, especially in production and isolation stages.

8. Challenges of phage therapy

Despite the numerous advantages of phage delivery as a possible response to antibiotic resistance, some challenges are currently being encountered, which must be addressed for better performance in future usage. Some of the current challenges, as well as the future avenues to explore the potential applications of bacteriophages, are discussed below.

8.1. Regulatory framework to ensure quality and safety of phage therapy

A robust regulatory framework for phage therapy is essential, requiring marketing authorization with evidence of quality, safety, and efficacy under good manufacturing practices (GMP) [180, 181]. However, strict GMP compliance demands significant financial resources, posing challenges for phage therapy institutions, particularly for patient-specific, customized phage preparations [20, 182]. Current regulations are better suited for industrial-scale production, and satisfactory frameworks for personalized phage therapy are still under discussion between phage sponsors and regulatory agencies. In re-

sponse, some European countries are developing national regulatory solutions [183]. Safety and quality are critical for successful phage therapy, necessitating strict guidelines akin to those for pharmaceuticals [184]. Proposed requirements include avoiding phages with lysogeny, virulence, or resistance factors; ensuring purity and consistency; and implementing quality control for sterility, pH, stability, and cytotoxicity [180, 183–185]. While progress has been made in developed countries, global approval of phage therapy still faces significant hurdles [181, 183].

8.2. Stability of phage preparations

The stability of phage preparations is key to success in phage therapy. A good phage preparation should have a good shelf life during processing and long-term storage [157, 186]. Alternative strategies to improve the storage shelf life of phages are important for therapeutic purposes because treatment efficacy depends on phage concentrations at the site of infection, protecting them from the harsh conditions found in the human body [187, 188]. Spontaneous mutations in phage stocks are an issue of concern [189] that must be addressed to ensure the stability of phages. Difficulty in the predictability of phage evolution during production is a major challenge that must be overcome for achievable phage therapy [180, 183].

8.3. Rapid Screening of Efficient Phages

Another challenging factor in phage therapy is developing fast, high-throughput screening methods to identify phages targeting specific bacteria, given their high specificity. Rapid screening is important in therapeutic contexts, necessitating alternatives to the

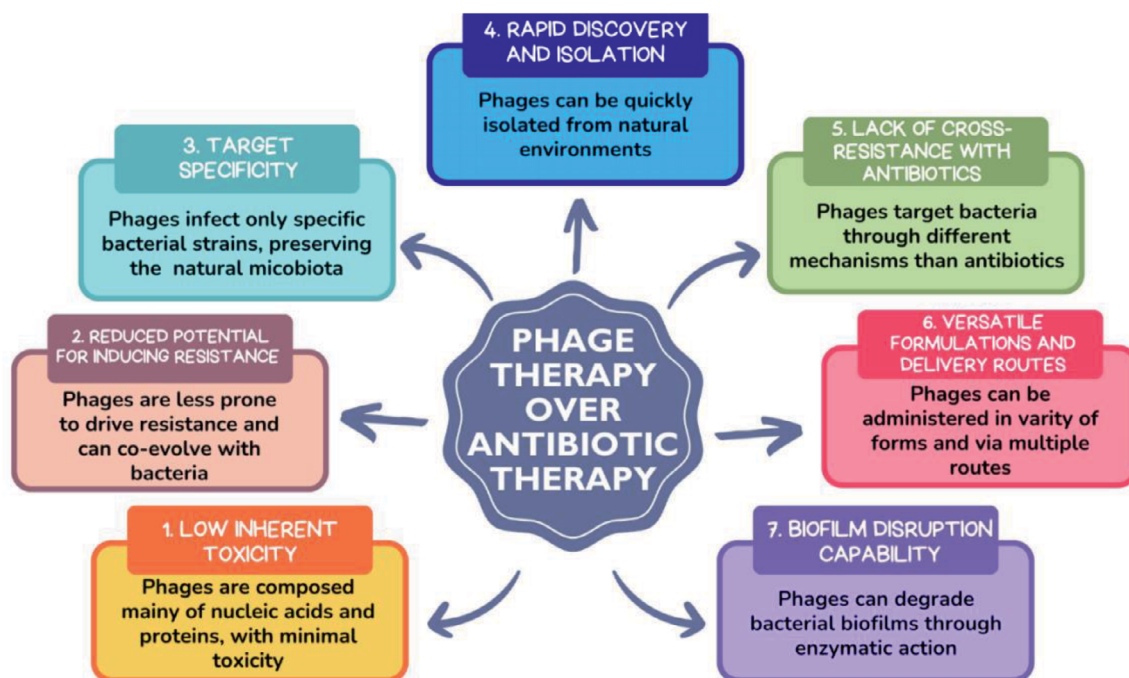


Fig. 4. Advantages of Phage Therapy over Antibiotic Therapy.

Рис. 4. Преимущества фаговой терапии перед антибиотикотерапией.

time-consuming traditional double-layer agar method for screening phage arrays against bacteria [183]. Numerous methods, offering qualitative or quantitative results through direct or indirect measurements, have been developed. These include flow cytometry to detect cells with low-density cell walls, real-time PCR (qPCR), measurement of enzyme release from phage-induced cell lysis, surface plasmon resonance (SPR) for quantifying molecules bound to surfaces [183], cell respiration to monitor bacterial growth [190], and optical density kinetics analysis for phage detection and quantification [191]. Despite their speed, these methods have their pitfalls, including complex technical requirements and high costs [183]. Future development of affordable, simple, and rapid high-throughput screening methods for clinical settings and phage banks is essential for the global acceptance of phage therapy.

8.4. Biofilm production and bacterial resistance

Bacteria in the human body tend to form biofilms, which are complex groups of surface-attached cells that are covered by a self-produced matrix that may slow down phage diffusion or adsorb phages, affecting their ability to infect bacterial cells [192–195]. Although some phages release depolymerases that degrade biofilms, the effectiveness of these is questionable because the interaction between phages and biofilms is intricate, and further research is required for effective treatment of infections against biofilms [183]. Bacteriophage-resistant mutants pose another challenge in phage therapy. Such mutants may occur due to superinfection exclusion, receptor modification, phage DNA degradation, cyclic oligonucleotide-mediated anti-phage systems, or abortive infection systems [196]. To circumvent resistance, countermeasures entail the use of phage cocktails to target heterogeneous bacterial receptors, replacing neutralized phages with active ones against resistant mutants, and combining phages with antibiotics or other antimicrobials to enhance efficacy and reduce resistance emergence [183, 197–199].

9. Future prospects

To combat antimicrobial resistance, novel remedies like phage therapy are being contemplated. Phages are already utilized to control bacterial growth in human beings, animals, the environment, and the food industry. Phages may be utilized in conjunction with enzymes or genetically engineered in the future. Although phage therapy has a vast potential, there have been fears that its widespread use may lead to resistance, just like antibiotics. However, this is countered by the reality that it is likely only applied in antibiotic failure and that there is also the possibility of tailored phage cocktails [183]. Hearteningly, natural co-evolution between phages and bacteria ensures an ongoing arms race, minimizing the potential for long-term bacterial resistance [183, 200]. Despite progress in science, extensive application of phage therapy is still handicapped by major obstacles. To make phage therapy universally accessible and affordable, combined efforts by scientists, clinicians, and countries are essential

to overcome regulatory and logistical barriers and to accelerate research and innovation even further.

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Received 20 January 2026

Accepted 17 March 2026

Published 30 April 2026

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Поступила 20.01.2026

Принята в печать 17.03.2026

Опубликована 30.04.2026