Harnessing Engineered Bacteriophages to Combat Antimicrobial Resistance: A Targeted Biomedical Approach to a Global Crisis

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Abstract
Antimicrobial resistance (AMR) is one of the biggest threats to global health. Every year, millions of people die because bacteria no longer respond to traditional antibiotics. Phage therapy offers a promising biomedical alternative. These viruses target specific bacteria, killing them while leaving others alone. They can multiply inside infections and even work against multidrug resistant strains. Engineered phages take this a step further. Modified through genetic techniques and CRISPR-Cas tools, they can tackle problems that natural phages struggle with, such as limited host ranges or stubborn biofilm infections. The biomedical evidence is encouraging. Preclinical studies and clinical trials show phages succeeding in treating burn wounds, infections related to cystic fibrosis, and diabetic foot ulcers. Combining phages with antibiotics often works better than either on its own, reducing bacterial loads more effectively. Challenges remain, though. Bacteria can develop resistance to phages, and better delivery methods are still needed. Recent advances, including AI-driven phage design, offer a way forward. By integrating these innovations, phage therapy could cut AMR-related deaths and make access to treatment more fair worldwide. This review draws on biomedical studies, highlighting successes as well as gaps, to guide future research in the field.

Keywords: Antimicrobial Resistance, Biomedical phage therapy, Bacteriophages, CRISPR, Multidrug-resistant

1. Introduction

The problem of antimicrobial resistance or AMR has become one of the current health issues of the greatest magnitude. It occurs when bacteria, viruses, fungi, or parasites evolve in a manner that reduces the effects of our medicines. The World Health Organization has categorized AMR among the top ten global public health threats (WHO bacterial priority pathogens list, 2024). There were almost 5 million deaths attributed to it in 2019 alone, 1.27 million due to resistant infections directly (Murray et al. 2021) And the situation is only getting worse. Common pathogens like *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Escherichia coli* are evolving rapidly, making even everyday infections harder to treat. Alexander Fleming, who discovered penicillin, warned about this back in 1945. He said that misuse of antibiotics would eventually lead to resistance—and today, we are seeing that warning come true, especially with multidrug-resistant bacteria (Fleming 1945).

Bacteriophages, or simply phages, are viruses that naturally attack bacteria and hold significant biomedical relevance. They were first described in 1915 by Frederick Twort and later by Felix d'Herelle (Twort 1915); (d'Herelle 1961). In the early 1900s, phages were even tested as treatments for infections, but once antibiotics like penicillin came along in the 1940s, phage therapy was largely abandoned (Egido et al. 2022); (Chakraborty et al. 2016). That picture is changing With antimicrobial resistance (AMR) climbing and fewer new antibiotics in the pipeline, interest in phage therapy has surged again (Kortright et al. 2019). Phages bring some clear advantages. They are highly specific, hitting harmful bacteria while sparing the beneficial ones. They can also replicate right at the infection site, which helps sustain their impact. And importantly, they remain effective against strains that no longer respond to antibiotics (Mishra et al. 2024; Sukirtha et al., 2025).

Nonetheless, natural phages are limited, such as having a limited ability to infect a host, and the possibility of bacteria developing resistance to the phage as well (Li et al. 2024) ; (Kalidass et al. 2025). That is where engineering comes into the picture. Recent developments in the field of synthetic biology enable us to alter these phages in order to enhance their usefulness (Tridgett et al. 2021). As an example, the ability to edit phage genomes with CRISPR-Cas can be used to increase the range of their targets and enhance the capability to overcome bacterial defenses (Cui et al. 2023); (Niranjan Kumar et al. 2026).

This review claims that the future of combating AMR lies in engineered phages (Sivaraj et al. 2026). We will discuss the AMR crisis in detail, how phages can be used as natural antimicrobials, engineering innovations including molecular

mechanisms of phage-antibiotic synergy and AI applications, clinical applications and trials, molecular interactions with the human host, challenges with emphasis on resistance mechanisms and translational barriers, and future directions. In the process, synergies with antibiotics and new technologies such as AI in designing phages are examined. At the conclusion, it will be clear why phage therapy has a chance to introduce a new era of targeted treatments, although key challenges must be overcome directly.

2. AMR Crisis

AMR happens when microbes build defenses against antibiotics, making them useless for treating infections. This is a huge global health problem, threatening current treatments and raising risks of disease spread and death (Niveda et al. 2024). The rise of "superbugs" drug-resistant bacteria makes treating common infections hard and complicates procedures like transplants, cancer therapy, and surgery (Almansour et al. 2023). The main drivers include excessive use and abuse of antibiotics in humans like self-medication and over-prescription of antibiotics and in animals for growth promotion (Ferrara et al. 2024). Poor sanitation and environmental pollution from farms or pharmaceutical factories accelerate the spread of resistant genes (Estany-Gestal, Salgado-Barreira, and Vazquez-Lago 2024); (Karthik Raja et al. 2025).

The numbers are alarming. AMR caused 4.95 million deaths worldwide in 2019, of which 1.27 million were direct results of resistant infections (Murray et al. 2021) ; (Chambers and Fowler 2022). Important culprits include *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Mycobacterium tuberculosis*, *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, and *Escherichia coli*. Methicillin-resistant *S. aureus* (MRSA) alone contributed more than 100,000 deaths. Third-generation cephalosporin-resistant *E. coli* and carbapenem-resistant *K. pneumoniae* posed additional major threats(Brüssow 2024). Geographic distribution varies, with *S. aureus* and *E. coli* more prevalent in high-income regions and *S. pneumoniae* and *K. pneumoniae* devastating sub-Saharan Africa.

The crisis is worsening due to the slow discovery of new antibiotics bacteria have developed resistance to almost every class despite hundreds on the market (Domingo-Calap and Delgado-Martínez 2018) ; (Raja et al. 2024).

Patient non-compliance, poor hygiene, and environmental runoff further aggravate the situation. AMR requires international efforts, yet it remains poorly addressed in many regions (Niveda et al. 2024). Phage therapy, which uses natural bacterial killers to specifically target pathogens rather than causing the broad damage of antibiotics, offers a viable alternative (Olawade et al. 2024). Phage-derived enzymes such as endolysins provide additional tools (Sabur et al. 2025) (Huda, Alam, and Sharma 2020).

Even a minor incision can become fatal if colonized by resistant bacteria, and MDR infections in hospital burn or wound sites frequently prove unresponsive to standard treatments. Phage therapy provides a potential escape route. Understanding the full dimensions of the AMR crisis—medical, economic, and social, with poorer countries affected mostis essential before valuing advanced phage-based solutions.

3. Bacteriophages: Nature's Targeted Antimicrobial

Bacteriophages, or phages, are viruses that specifically attack and lyse bacterial cells, making them potential antimicrobial agents. They have been studied for therapeutic uses since the early 20th century, especially before antibiotics became widespread (Twort 1915); (d'Herelle 1961).But with antibiotics' rise, phage therapy faded (Kortright et al. 2019). Unlike broad-spectrum antibiotics, phages have remarkable specificity for their bacterial hosts. This lets them eliminate harmful strains while sparing useful microbiota (Principi, Silvestri, and Esposito 2019). Phages were first used therapeutically in 1919 against *Shigella dysenteriae*, and they are the most abundant biological entities on Earth, with 10^{31} –10^{32} phages at any time. They regulate bacterial populations, killing 20–40% of bacteria in ocean surface waters daily (Goodridge 2013).

How do they work? Phages bind to bacterial surface receptors, inject their genome DNA or RNA in a protein capsid, and use the host's machinery to multiply. This causes cell lysis, releasing new phages (Egido et al. 2022). Two dominant cycles exist: the lytic cycle, during which the bacterium ruptures quickly, and the lysogenic cycle, during which phage DNA integrates and remains inactive (Faruk et al. 2025). Lytic phages are preferred for therapy since they kill without integrating.

Phages have several benefits. They self-reproduce, so even a small dose amplifies at the infection site. They show low toxicity because they do not infect human cells. They also co-evolve with bacteria and adapt to new resistances (Mishra et al. 2024). Recent literature points to applications in wound infections, respiratory diseases, gastrointestinal diseases, sepsis, and biofilms (Faruk et al. 2025). Endolysins and phage-derived enzymes can also be used as antimicrobials on their own (Murray et al. 2021).

But natural phages are not ideal. Host defenses and low host range restrict their use. That is why engineering is key. Genetic modification and bioinformatics tools are used to develop phage cocktails and decrease resistance (Uchechukwu and Shonekan 2024). For example, phages may be engineered to attack MDR biofilm pathogens or intracellular infections (Eghbalpoor et al. 2024). With continued research, phages may become common in medicine, but more funding and partnerships are required to bridge lab work and clinical practice (Sivalingam and Arjun 2024).

Phages also have ecological functions, regulating bacterial populations in natural environments. This natural balance inspires their medical use. However, to fully exploit them, engineering is essential, as the following section elaborates.

4. Advances in Phage Engineering

Modified phages have shown the capability to address many challenges posed by natural phages and conventional antibiotics when combating biofilm-producing, extensively drug-resistant (XDR), and multidrug-resistant (MDR) bacteria (Eghbalpoor et al. 2024). Genetic engineering makes phages more potent against AMR. Natural phages are

effective but frequently limited in target range or susceptible to bacterial resistance. Engineered phages, also known as designer phages, overcome this (Lewis, Williams, and Sagona 2024). For example, tail fibers can be modified to increase host ranges, enabling phages to infect additional bacteria (Egido et al. 2022). Personalized engineered phages have been demonstrated to be successful when antibiotics fail in a multinational study of 100 cases (Pirnay et al. 2024).

CRISPR-Cas integration is one of the major developments. These systems allow phages to cut bacterial DNA more accurately, increasing the rate of kills (Khambhati et al. 2023). Gencay et al. (2024) designed SNIPR001, a cocktail consisting of modified tail fibers and CRISPR, which is more efficient in clearing *E. coli* biofilms than natural phages in mice and minipigs (Gencay et al. 2024). Other examples include Yosef et al. (2015), who reprogrammed phages to target resistant bacteria, and Lu and Collins (2007), who added phage-encoded enzymes to disrupt biofilms (Yosef et al. 2015) ; (Lu and Collins 2007). Ando et al. (2015) used yeast to edit phage genomes, allowing *E. coli* phages to target *Klebsiella* (Ando et al. 2015).

Phage-antibiotic synergy (PAS) is particularly promising. Combinations re-sensitize bacteria to drugs. At low doses, Kebriaei et al. (2023) wiped out MRSA biofilms with a three-phage mix plus antibiotics (Kebriaei et al. 2023). Gordillo Altamirano et al. (2022) demonstrated that phage øFG02 reinstated ceftazidime activity against *A. baumannii* (Gordillo Altamirano et al. 2022). Anand et al. (2020) showed that phage VTCCBPA43 reduced *K. pneumoniae* lung loads in mice after a single dose (Anand et al. 2020). These works highlight how engineering circumvents issues such as resistance and host range (Cui et al. 2023).

Molecular mechanisms of PAS include: (1) cell-wall antibiotics causing bacterial filamentation or morphological changes that increase phage adsorption sites and burst size; (2) phages disrupting biofilms, capsules, or efflux pumps, restoring antibiotic penetration and intracellular accumulation; (3) dual selective pressures creating evolutionary fitness trade-offs that slow resistance evolution (Supina and Dennis 2025). Compatibility efficiency varies by antibiotic class that is stronger synergy with beta-lactams; potential antagonism with some protein-synthesis inhibitors and requires screening via checkerboard assays, time-kill curves, and mechanism-based models. Strain-specific testing is essential for optimal pairing and dosing ratios.

In addition to infections, engineered phages are under investigation for use as vaccines, in cancer therapy, and for gene delivery. Phage display improves immunizations (Zalewska-Piątek and Piątek 2021). They serve as vectors for accurate CRISPR gene delivery (Wang et al. 2024) and can specifically attack tumours to promote immunity (Islam, Fan, and Pan 2023). Challenges remain in stability and safety, with the possibility of bacterial resistance to modified phages requiring continuous monitoring. Recent reviews focus on AI to predict interactions and optimize cocktails (Khambhati et al. 2023). Engineering transforms phages into multi-purpose weapons.

In 2024-2025, engineering for intracellular bacteria and AI-optimized therapy have advanced (Cui et al. 2023) ; (Doud, Robertson, and Strathdee 2025). AI algorithms, including deep learning and genome language models (e.g., Evo), are trained on large phage/bacterial genome datasets to predict host range, adsorption, and immunogenicity. Generative models design novel functional phages, as seen in synthetic ΦX174 variants with improved *E. coli* infectivity. These build on previous research and broaden phage applications.

Genetic modification and bioinformatics advantages: Tail-fiber engineering and bioinformatics expand host range by altering receptor-binding proteins and predicting anti-defense genes. These reduce resistance development by enabling multi-receptor targeting and rapid cocktail adaptation. Preclinical data and compassionate-use cohorts (~100 cases) support improved efficacy against MDR strains, though clinical trial data for engineered versions remain limited and highlight the need for further translation.

5. Clinical Applications and Trials

Phage therapy has moved from the laboratory into the clinical setting, with promising results against MDR infections. Modern tests on safety and efficacy date back to 1919 when *Shigella* was first used (Goodridge 2013).

The PhagoBurn project, an EU initiative, ran phase 1/2 trials in nine burn centers. It tested lytic *P. aeruginosa* phage PP1131 for burn wounds with daily topical applications. Results showed low concentrations cleared bacteria slower than standard care, leading to termination and highlighting the need for better dosing (Huang et al. 2021). Armata Pharmaceuticals' SWARM-P.a. trial (phase 1b/2a) tested AP-PA02 for *P. aeruginosa* in cystic fibrosis and bronchiectasis when inhaled. It showed safety, tolerability, good lung targeting with low systemic exposure, and progression to phase 2b (Sharma 2024).

Locus Biosciences' LBP-EC01 uses CRISPR–Cas3 to damage bacterial DNA for antibiotic-resistant *E. coli* UTIs. The ELIMINATE phase 2/3 trial checks safety, pharmacokinetics, and efficacy. Early results show *E. coli* levels dropped in four hours, with symptoms gone by day 10 (Kim et al. 2024). MB Pharma's DUOFAG® cocktail targets *P. aeruginosa* and *S. aureus* for diabetic foot infections. Genetic studies confirm efficacy against clinical isolates and it is GMP-certified (Sawa, Moriyama, and Kinoshita 2024). A bibliometric analysis reviewed 6,538 works on phage therapy, with output rising sharply and 45 trials noted by March 2023. Compassionate uses for MDR *E. coli* UTIs showed 80–90% success. Regulations vary globally, with challenges in dosing and 10–15% resistance (Maimaiti et al. 2022).

The Israeli Phage Therapy Center reported compassionate use of PASA16 in 16 *P. aeruginosa* patients. Local and IV treatments led to positive outcomes in 13 of 15 patients (86.6%), with synergy in resistant cases (Onallah et al. 2023). TechnoPhage's TP-122A targets *P. aeruginosa* in ventilator-associated pneumonia via nebulization. A comprehensive review analyzed 59 studies covering 2,241 patients, reporting 77.2% symptomatic recovery and 67% pathogen eradication with mild side effects (Uyttebroek et al. 2022).

Adaptive Phage Therapeutics' DANCE™ trial tests phage for diabetic foot osteomyelitis, and the PHAGE study evaluates

WRAIR-PAM-CF1 in cystic fibrosis (Sawa et al. 2024) ; (vasundhara 2023). Recent systematic studies confirm efficacy in diabetic foot ulcers with safe outcomes (Young et al. 2023). In children, phage therapy shows promise but needs more data (Strathdee et al. 2023). Personalized approaches, like inhaled phages, affect clinical endpoints (Elfadadny et al. 2025).

6. Molecular Interaction of Phage Therapy in Human Host

Phage therapy works at multiple levels of the human body. It acts by the direct killing of bacteria which regulates the natural immune response and alters the adaptive immune response. The process involves a bacteriophage entering its bacterial target, executing the lytic cycle, and lysing the cell, spilling out progeny phages and bacterial debris. This leads to host reactions involving recognition of bacterial products including lipopolysaccharides (LPS), peptidoglycan fragments, and CpG-containing DNA. Host pattern-recognition receptors detect these signatures. For example, TLR4 recognizes LPS and triggers NF-κB signaling, leading to production of inflammatory agents such as TNF-α, IL-6 and IL-1 (Kortright et al. 2019). TLR9 identifies CpG motifs (Kaźmierczak et al. 2021), cytosolic cGAS-STING enhances type I responses, and NOD1/NOD2 activate inflammasome pathways maturing IL-1β and IL-18 (Bichet et al. 2021).

Innate immunity does not always react predictably. Some bacteriophages bypass canonical DNA sensing pathways. Bichet et al. (2021) demonstrated that T4 phages can be internalized by mammalian cells through macropinocytosis without triggering cGAS–STING, instead activating Akt/PKB signaling. T4 and T7 phages are often anti-inflammatory, while filamentous Pf phages from *Pseudomonas aeruginosa* can be pro-inflammatory on airway epithelia (Van Nieuwenhuyse et al. 2022). Zamora et al. (2024) showed airway epithelial cells change transcriptional programs and cytokine secretion in phage-type and environment-dependent ways, underscoring the need to consider diversity in therapeutic design (Zamora et al. 2024).

Adaptive immunity involves dendritic cells presenting antigens to T cells via MHC class II (CD4+) and cross-presentation (CD8+), while B cells secrete antibodies against phage capsid proteins (Roche and Furuta 2015). Washizaki et al. (2024) demonstrated that therapeutic phages induce neutralizing antibodies that lower half-life and remodel pharmacokinetics, implying that immune memory to phages influences repeated dosing success (Washizaki, Sakiyama, and Ando 2024).

Clearance pathways differ: Kupffer cells, splenic macrophages, and renal filtration remove phages, with small Podoviridae cleared faster than larger Myoviridae (Kornienko et al. 2020). Interestingly, not all phage families clear according to size; these variations affect treatment efficacy and dosing intervals.

Many phages act as immunomodulators that reduce inflammation (Sweere et al. 2019). In contrast, antibiotics frequently worsen dysbiosis. A key example is the compassionate use of modified mycobacteriophages in a cystic fibrosis patient with disseminated *M. abscessus* (Dedrick et al. 2019). The treatment controlled bacterial load without excessive inflammation, likely due to balanced lysis and immunoregulatory properties. Phage therapy outcomes depend on a web of interactions, and acknowledging diversity is essential for repeatable clinical approaches (Podlacha et al. 2021). Significant differences in immunogenicity exist; more research is necessary to fully understand immune regulation and therapeutic potential (Champagne-Jorgensen et al. 2023).

Long-term safety and immunogenicity data are limited but generally show mild, transient effects. Neutralizing antibodies can emerge with repeated administrations, shortening phage half-life; strategies include cocktail rotation and engineering for reduced immunogenicity. No major chronic toxicities have been widely reported in monitored settings, but longitudinal studies are needed.

7. Challenges and Future Directions

Despite successes, phage therapy has biological and systemic challenges. Phage resistance appears in 10–15% of cases, needing adaptive strategies like cocktails or AI design (Bleriot et al. 2024). The molecular basis of bacterial resistance includes receptor modification (mutations masking adsorption sites), restriction-modification systems (DNA cleavage), bacterial CRISPR arrays (spacer-guided cleavage), abortive infection (host suicide), and defense islands imposing fitness costs. Immunogenicity and delivery optimization remain key gaps (Champagne-Jorgensen et al. 2023). Regulatory differences hinder global use (Maimaiti et al. 2022). A recent review stresses re-evaluating unsuitable phages with virulence or transduction risks (Cook and Hynes 2025).

Delivery is tricky. Phages must avoid immune elimination and reach infection sites. Intravenous suits systemic infections, but topical or inhaled routes are often more effective for wounds or lungs due to higher local concentrations and sustained retention supported by preclinical bacterial load reductions and clinical PK data from inhaled formulations. Long-term attenuation can result from immunogenicity (Sawa et al. 2024). Ethical supervision, including COPE guidelines for data integrity, is critical.

Future paths include AI for phage-host predictions to cut resistance (Doud et al. 2025). Cocktails broaden ranges (Gencay et al. 2024). Global harmonization through WHO could streamline access in LMICs (Olawade et al. 2024). Beyond therapy, phages show promise for vaccines or cancer (Islam et al. 2023). Tailored approaches work in children (Strathdee et al. 2023) and diabetic ulcers (Young et al. 2023). Personalized inhaled therapies could transform care (Elfadadny et al. 2025). These could halve AMR deaths by 2035 if scaled (Zalewska-Piątek and Piątek 2021), but investment is crucial.

Translational barriers: Animal models (often murine) show strong efficacy but differ from humans in immune responses, microbiome, and infection dynamics. Challenges include GMP scaling, predicting human PK/PD, and accounting for comorbidities. Interdisciplinary collaboration is required across microbiology, genetics, bioinformatics/AI, clinical medicine, immunology, and regulatory/public health sciences. Specific plans involve AI-optimized personalized cocktails, sustained-delivery systems, large RCTs of engineered combinations, and WHO-supported harmonization for

equitable access.

8. Conclusion

The AMR outbreak requires new solutions and bacteriophage therapy addresses the challenge. Between the natural phages' selectivity and the increased power of engineered ones, this method brings hope when antibiotics fail. There is clinical evidence, both in trials such as ELIMINATE and PhagoBurn, and compassionate successes, that it is able to treat MDR infections at high rates, typically 80-90% (Uyttebroek et al. 2022) ; (Onallah et al. 2023). Antibiotic synergies have an amplifying effect, yet this method makes bacteria more sensitive and gradually slows resistance (Kebriaei et al. 2023). Still, there are hurdles to overcome. Bacteria can develop resistance to phages, delivery methods need fine-tuning, and regulations vary from country to country. But future proceedings like AI-driven phage design and stronger global collaboration could help overcome these issues (Venkataraman et al. 2025). Phage therapy should not be seen as just a backup plan. It has the potential to drive personalized medicine, support vaccine development, and even promote health equity. With antimicrobial resistance taking more than 1.27 million lives each year, mostly in low and middle income countries, phages could be game-changing (Salam et al. 2023).

What's needed now is more research, greater investment, and clear policy support to bring them into mainstream biomedical practice. In many ways, phages represent a return to nature's own solutions refined through modern science to take on one of the greatest health threats humanity faces today.

Future Scope and Implications

The revival of phage therapy comes at a perfect time, as AMR links to over 1.27 million deaths annually, hitting LMICs hardest (Salam et al. 2023). Clinical evidence keeps proving phages work against drug-resistant infections. Their future lies not only as alternatives but also as catalysts for personalized treatments, better health equity, and smarter antibiotic use. Phage therapy is poised to grow thanks to new regulations and technologies. WHO is urging countries to include phages in AMR plans. Standard ways to produce and distribute them are needed, especially where resistance is deadliest. Tools like CRISPR-edited phages and AI-designed ones could lower resistance (seen in 1 in 10 cases) and make treatments affordable (Khambhati et al. 2023) ; (Venkataraman et al. 2025).

To make phage therapy impactful, rules must be streamlined and infrastructure built. Emerging areas include phages for oral health, cancer, and plant diseases (Pirnay et al. 2024) ; (Islam et al. 2023). With advances in anti-phage strategies understood, better therapies can be designed (Zalewska-Piątek and Piątek 2021). The potential is vast, but action is key.

Additional Discussion: Ethical and Practical Considerations

Phage therapy should adhere to guidelines such as COPE to avoid plagiarism and data fabrication. Informed consent is essential, particularly in compassionate uses. They have good safety profiles with limited side effects, although long-term monitoring is required (Petrovic Fabijan et al. 2020). GMP production can be scaled but remains challenging, as with DUOFAG (Sawa et al. 2024). Implementation in resource-limited environments should include economic feasibility evaluations.

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Ethics and consent to participate

Not applicable

Consent to Publish

Not Applicable

Authors Contributions

Mohammad Umaid: Conceptualization, Formal analysis, Writing – Original draft.
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The authors declare no competing interests.

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Table 1 compares key studies, showing outcomes and advantages. (Populate with entries from Gencay et al. 2024, Kebriaei et al. 2023, etc., including model, outcomes like log CFU reduction, and advantages/limitations.)

Reference	Engineering Strategy	Target Pathogen	Model / Stage	Primary Outcomes	Advantages / Limitations
(Gencay et al. 2024)	CRISPR-Cas + modified tail fibers (SNIPR001 cocktail of 4 phages)	*E. coli* (including biofilms)	Mice & minipigs (preclinical); Phase 1 clinical	Significant reduction in *E. coli* burden (up to several $\log_{10}$ CFU/g in gut); better biofilm clearance than wild-type phages; well tolerated with GI restriction	Expanded host range + reduced resistance emergence; minimal microbiome disruption; still early clinical data
(Kebriaei et al. 2023)	Multi-phage cocktail (3 phages) + antibiotics (PAS)	MRSA (biofilms)	In vitro biofilm models	Complete eradication of MRSA biofilms at low doses	Strong synergy with antibiotics; lower doses needed; limited in vivo data
(Gordillo Altamirano et al. 2022)	Natural phage øFG02 (engineered context)	*A. baumannii*	In vitro & preclinical	Restored ceftazidime susceptibility; significant bacterial killing	Re-sensitization of resistant strains; needs combination testing
(Anand et al. 2020)	Phage VTCCBPA43	*K. pneumoniae*	Mouse lung infection model	Significant reduction in lung bacterial load after single dose	Effective against respiratory MDR; single-dose potential
(Lu and Collins 2007)	Phage-encoded enzymes (depolymerases)	Biofilm-forming bacteria	In vitro	Enhanced biofilm disruption	Improved penetration; older study, needs modern engineering
(Yosef et al. 2015)	Reprogrammed phages targeting resistance plasmids	Resistant *E. coli*	In vitro & preclinical	Selective killing of resistant bacteria	Reduced resistance spread; early proof-of-concept

Table 2 summarizes trials. (Populate with trial name, phage/engineering, target, phase, key outcomes like bacterial reduction percentages or success rates, and references such as Kim et al. 2024, Onallah et al. 2023.)

Trial / Product	Phage Type / Engineering	Target Pathogen / Infection	Phase / Design	Key Outcomes	Reference
PhagoBurn (PP1131)	Lytic *P. aeruginosa* cocktail (natural)	Burn wound infections	Phase 1/2, randomised, controlled	Safety confirmed; slower bacterial clearance at low doses vs. standard care; trial terminated early due to dosing issues	Jault et al. (implied in (Huang et al. 2021)
SWARM-P.a. (AP-PA02)	Multi-phage cocktail (inhaled)	*P. aeruginosa* in CF / bronchiectasis	Phase 1b/2a	Good safety & tolerability; lung targeting with low systemic exposure; bacterial load	(Sharma 2024)

Trial / Product	Phage Type / Engineering	Target Pathogen / Infection	Phase / Design	Key Outcomes	Reference
				reduction signals	
ELIMINATE (LBP-EC01)	CRISPR-Cas3-enhanced 6-phage cocktail	Antibiotic-resistant *E. coli* UTI	Phase 2 Part 1 (open-label)	Rapid *E. coli* reduction (within 4 hours); symptom resolution; microbiologic improvement in ~87.5%; good tolerability	(Kim et al. 2024)
SNIPR001	CRISPR-Cas-armed + tail-fiber modified (4-phage cocktail)	*E. coli* gut colonization	Phase 1 (dose-escalation)	Well tolerated; dose-dependent *E. coli* reduction (up to 78% at highest dose vs. placebo); GI-restricted	(Gencay et al. 2024)& follow-up Phase 1 data
PASA16 (Israeli Center)	Specific *P. aeruginosa* phage (compassionate)	Refractory *P. aeruginosa* infections	Compassionate use (case series)	Positive clinical outcomes in 13/15 evaluable patients (86.6%); synergy with antibiotics; mild side effects	(Onallah et al. 2023)
DUOFAG®	Cocktail (2 *S. aureus* + 1 *P. aeruginosa*)	Diabetic foot infections	Clinical evaluation / GMP-certified	Efficacy against clinical isolates; safe profile	(Sawa et al. 2024)

Table 3 summarizes the family-specific immune pathways of therapeutic phages in the human host with clinical implications. (Populate with phage family, pathways (e.g., TLR4/NF-κB), outcomes, and mitigation strategies like rotation for repeated dosing.)

Phage Family / Example	Key Interaction Pathways	Immunological Outcome	Clinical Implications / Mitigation Strategies	Reference(s)
T4 (Myoviridae)	Macropinocytosis; minimal cGAS-STING; Akt/PKB activation	Often anti-inflammatory; modulates cell survival & cycle	Lower pro-inflammatory risk; suitable for systemic use; monitor repeated dosing	(Bichet et al. 2021)
T7	Variable PRR activation	Generally anti-inflammatory	Reduced tissue damage potential; combine with monitoring	(Kortright et al. 2019)
Filamentous Pf (from *P. aeruginosa*)	Airway epithelial activation	Pro-inflammatory cytokine secretion	Caution in respiratory infections; phage-type specific design needed	(Van Nieuwenhuyse et al. 2022) ; (Zamora et al. 2024)
General lytic phages	TLR4 (LPS), TLR9 (CpG), NOD1/2, cGAS-STING; NF-κB & inflammasome	Pro-inflammatory (PAMP release) + possible neutralization by antibodies	Risk of cytokine response or reduced efficacy on repeat; use cocktails or rotation	(Washizaki et al. 2024) ; (Sweere et al. 2019)
Mycobacteriophages (engineered)	Controlled lysis + immunomodulation	Balanced response; minimal excessive inflammation	Successful in compassionate use (e.g., CF *M. abscessus*);	(Dedrick et al. 2019)

Phage Family / Example	Key Interaction Pathways	Immunological Outcome	Clinical Implications / Mitigation Strategies	Reference(s)
			engineering for stealth	

Figure 1 provides a visual overview of this journey, from basic phage biology to real-world applications of engineered phages against AMR pathogens.

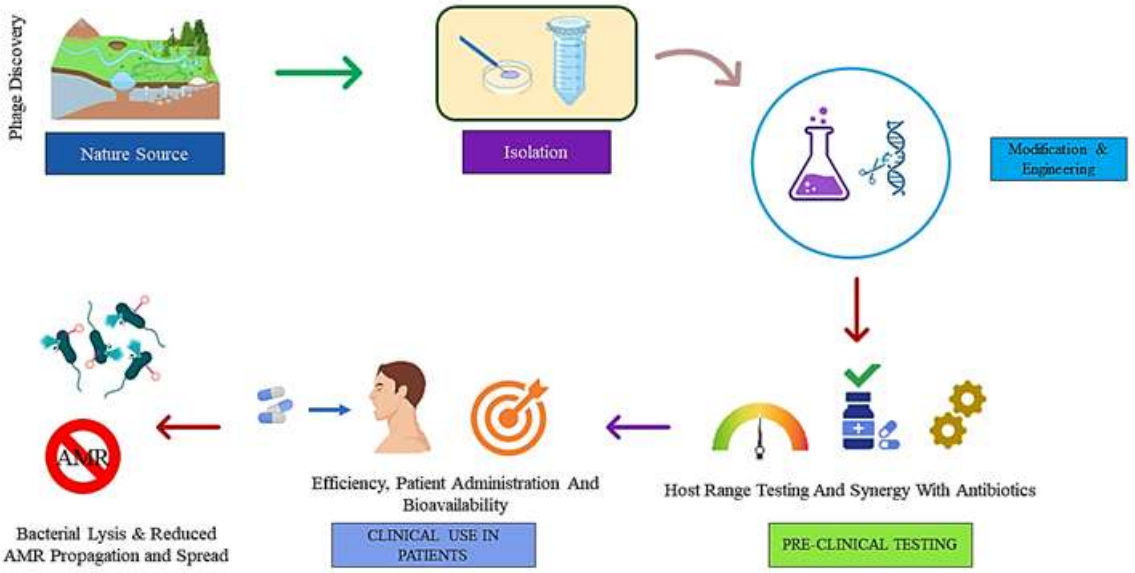


Figure 2: Diversity of Bacteriophages. This diagram classifies phages into types like tailed, filamentous, and polyhedral, with labels for DNA/RNA genomes and host-binding structures. It connects each type to AMR examples, such as tailed phages targeting MRSA.

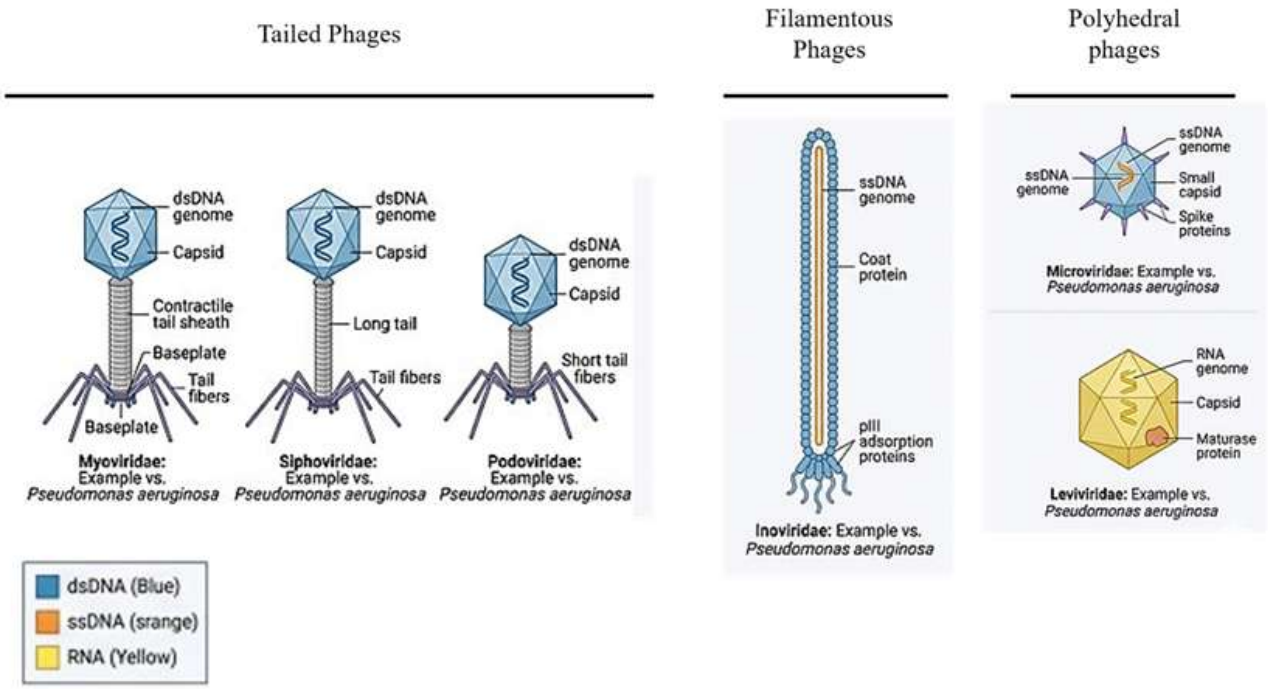


Figure 3: Lytic and Lysogenic Cycles of Bacteriophages. This figure illustrates the steps of each cycle: attachment, injection, replication, assembly, and lysis for lytic; integration and prophage state for lysogenic.

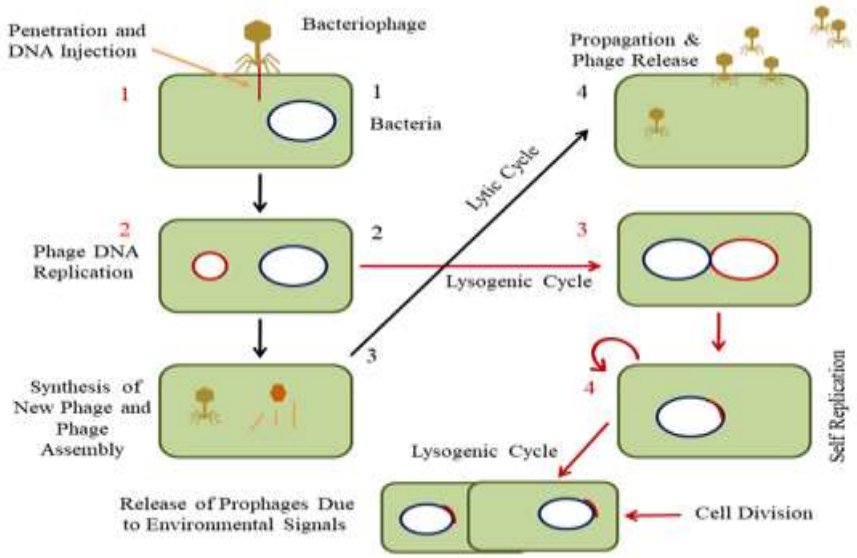


Figure 4: Schematic overview of the host immune response to phage therapy. Bacteriophage-mediated lysis of target bacteria releases pathogen-associated molecular patterns (PAMPs), including lipopolysaccharide (LPS), peptidoglycan (PGN), and CpG DNA.

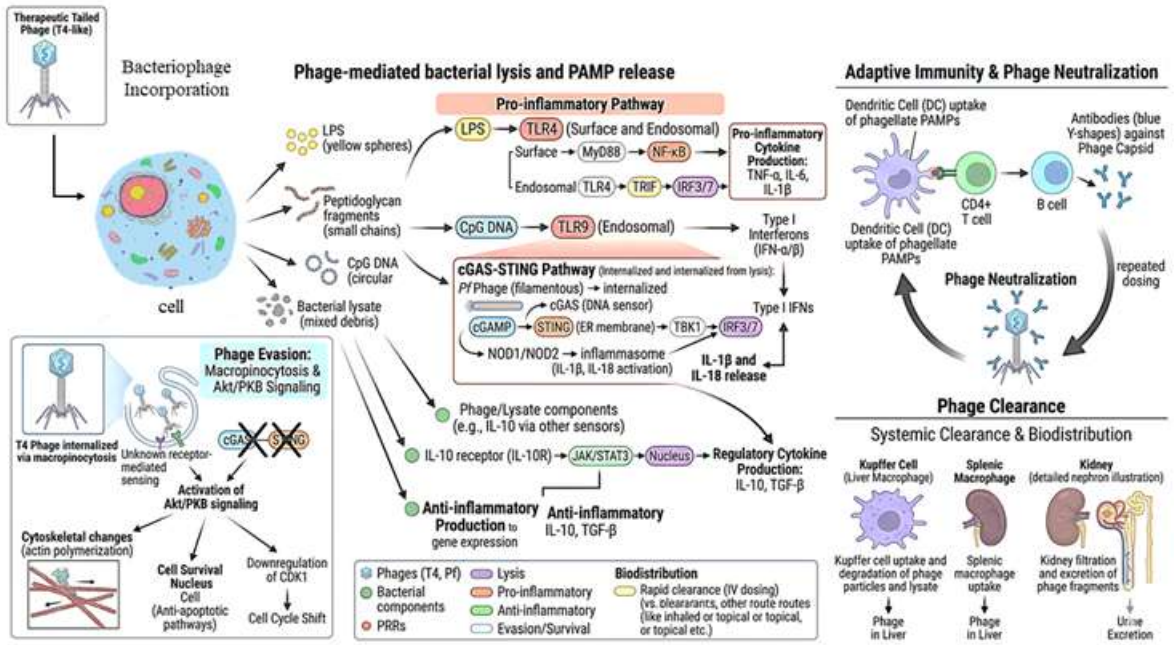


Figure 5: Intracellular sensing of bacteriophages and molecular interactions of therapeutic phages in the human host.

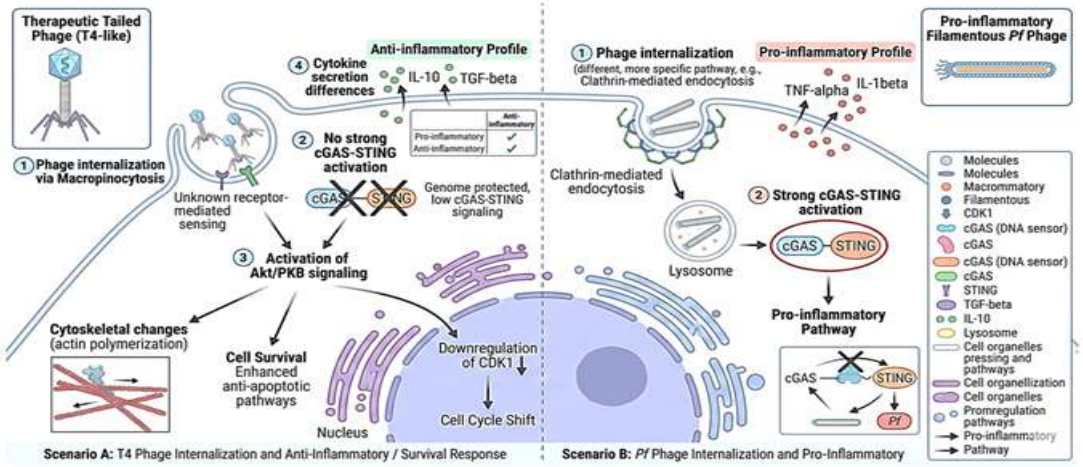
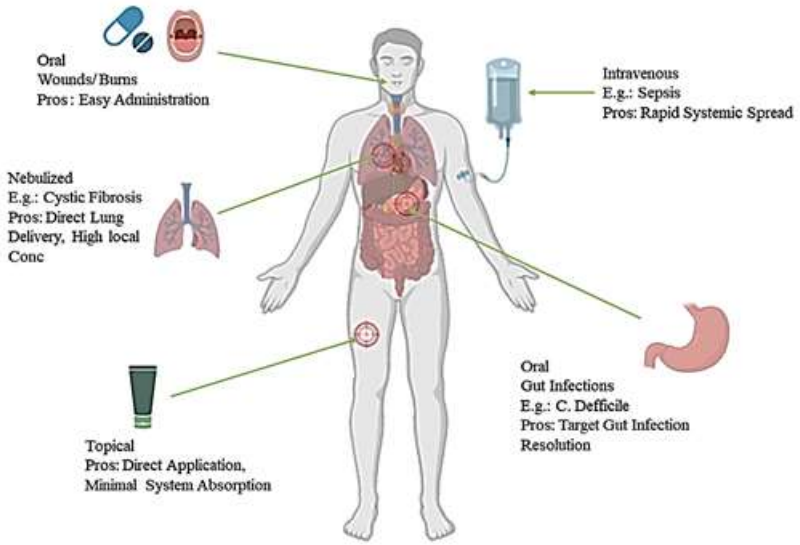


Figure 6: Phage Delivery Routes. This diagram depicts routes like intravenous (for sepsis), topical (for wounds), nebulized (for lungs), and oral (for gut). Each is linked to examples, with pros like rapid systemic spread vs. local concentration and supporting efficacy data.



References

1. Almansour, Ayidh M., Meshari A. Alhadlaq, Khaloud O. Alzahrani, Lenah E. Mukhtar, Abdulmohsen L. Alharbi, and Sulaiman M. Alajel. 2023. "The Silent Threat: Antimicrobial-Resistant Pathogens in Food-Producing Animals and Their Impact on Public Health." *Microorganisms* 11(9):2127.
2. Anand, Taruna, Nitin Virmani, Sudarshan Kumar, Ashok Kumar Mohanty, S. Pavulraj, Bidhan Ch Bera, Rajesh K. Vaid, Umang Ahlawat, and B. N. Tripathi. 2020. "Phage Therapy for Treatment of Virulent Klebsiella Pneumoniae Infection in a Mouse Model." *Journal of Global Antimicrobial Resistance* 21:34–41.
3. Ando, Hiroki, Sebastien Lemire, Diana P. Pires, and Timothy K. Lu. 2015. "Engineering Modular Viral Scaffolds for Targeted Bacterial Population Editing." *Cell Systems* 1(3):187–96. doi:10.1016/j.cels.2015.08.013.
4. Bichet, Marion C., Wai Hoe Chin, William Richards, Yu-Wei Lin, Laura Avellaneda-Franco, Catherine A. Hernandez, Arianna Oddo, Oleksandr Chernyavskiy, Volker Hilsenstein, Adrian Neild, Jian Li, Nicolas Hans Voelcker, Ruzeen Patwa, and Jeremy J. Barr. 2021. "Bacteriophage Uptake by Mammalian Cell Layers Represents a Potential Sink That May Impact Phage Therapy." *iScience* 24(4):102287. doi:10.1016/j.isci.2021.102287.
5. Bleriot, Inés, Olga Pacios, Lucia Blasco, Laura Fernández-García, María López, Concha Ortiz-Cartagena, Antonio Barrio-Pujante, Rodolfo García-Contreras, Jean-Paul Pirnay, Thomas K. Wood, and María Tomás. 2024. "Improving Phage Therapy by Evasion of Phage Resistance Mechanisms." *JAC-Antimicrobial Resistance* 6(1):dlae017. doi:10.1093/jacamr/dlae017.
6. Brüssow, Harald. 2024. "The Antibiotic Resistance Crisis and the Development of New Antibiotics." *Microbial Biotechnology* 17(7):e14510. doi:10.1111/1751-7915.14510.
7. Chakraborty, Chiranjib, Ashish Ranjan Sharma, Bidhan Chandra Patra, Manojit Bhattacharya, Garima Sharma, and Sang-Soo Lee. 2016. "MicroRNAs Mediated Regulation of MAPK Signaling Pathways in Chronic Myeloid Leukemia." *Oncotarget* 7(27):42683–97. 10.18632/oncotarget.7977.
8. Chambers, Henry F., and Vance G. Fowler. 2022. "Confronting Antimicrobial Resistance Together." *American Journal of Physiology - Lung Cellular and Molecular Physiology* 323(5):L643–45. doi:10.1152/ajplung.00327.2022.
9. Champagne-Jorgensen, Kevin, Tiffany Luong, Taylor Darby, and Dwayne R. Roach. 2023. "Immunogenicity of Bacteriophages." *Trends in Microbiology* 31(10):1058–71. doi:10.1016/j.tim.2023.04.008.
10. Cook, Bradley W. M., and Alexander P. Hynes. 2025. "Re-Evaluating What Makes a Phage Unsuitable for Therapy." *Npj Antimicrobials and Resistance* 3:45. doi:10.1038/s44259-025-00117-z.
11. Cui, Longzhu, Srivani Veeranarayanan, Kanate Thitiananpakorn, and Dhammika Leshan Wannigama. 2023. "Bacteriophage Bioengineering: A Transformative Approach for Targeted Drug Discovery and Beyond." *Pathogens* 12(9):1179. doi:10.3390/pathogens12091179.
12. Dedrick, Rebekah M., Carlos A. Guerrero-Bustamante, Rebecca A. Garlena, Daniel A. Russell, Katrina Ford, Kathryn Harris, Kimberly C. Gilmour, James Soothill, Deborah Jacobs-Sera, Robert T. Schooley, Graham F. Hatfull, and Helen Spencer. 2019. "Engineered Bacteriophages for Treatment of a Patient with a Disseminated Drug-Resistant Mycobacterium Abscessus." *Nature Medicine* 25(5):730–33. doi:10.1038/s41591-019-0437-z.
13. Domingo-Calap, Pilar, and Jennifer Delgado-Martínez. 2018. "Bacteriophages: Protagonists of a Post-Antibiotic Era." *Antibiotics* 7(3):66.
14. Doud, Michael B., Jacob M. Robertson, and Steffanie A. Strathdee. 2025. "Optimizing Phage Therapy with Artificial Intelligence: A Perspective." *Frontiers in Cellular and Infection Microbiology* 15. doi:10.3389/fcimb.2025.1611857.

15. Eghbalpoor, Fatemeh, Mahdieh Gorji, Maryam Zamani Alavigeh, and Majid Taati Moghadam. 2024. “Genetically Engineered Phages and Engineered Phage-Derived Enzymes to Destroy Biofilms of Antibiotics Resistance Bacteria.” *Heliyon* 10(15):e35666. doi:10.1016/j.heliyon.2024.e35666.
16. Egido, Julia E., Ana Rita Costa, Cristian Aparicio-Maldonado, Pieter-Jan Haas, and Stan JJ Brouns. 2022. “Mechanisms and Clinical Importance of Bacteriophage Resistance.” *FEMS Microbiology Reviews* 46(1):fuab048.
17. Elfadadny, Ahmed, Rokaia F. Ragab, Osama Aldesoky Abd Alaziz, Habiba Y. Essa, Esraa M. Eltony, Mohamed M. Ammar, and Wedad M. Nageeb. 2025. “Bacteriophage Therapy in Clinical Practice: Case Studies of Pseudomonas Aeruginosa Infections.” *Journal of Chemotherapy* 1–12.
18. Estany-Gestal, Ana, Angel Salgado-Barreira, and Juan Manuel Vazquez-Lago. 2024. “Antibiotic Use and Antimicrobial Resistance: A Global Public Health Crisis.” *Antibiotics* 13(9):900.
19. Faruk, Omor, Zilhas Ahmed Jewel, Sanjoy Bairagi, Mohammad Rasheduzzaman, Hindol Bagchi, Akber Subahan Mahbub Tuha, Imran Hossain, Ayon Bala, and Sarafat Ali. 2025. “Phage Treatment of Multidrug-Resistant Bacterial Infections in Humans, Animals, and Plants: The Current Status and Future Prospects.” *Infectious Medicine* 100168.
20. Ferrara, Francesco, Tommaso Castagna, Beatrice Pantolini, Maria Chiara Campanardi, Martina Roperti, Alessandra Grotto, Martina Fattori, Lucia Dal Maso, Federica Carrara, Giulia Zambarbieri, Andrea Zovi, Maurizio Capuozzo, and Roberto Langella. 2024. “The Challenge of Antimicrobial Resistance (AMR): Current Status and Future Prospects.” *Naunyn-Schmiedeberg’s Archives of Pharmacology* 397(12):9603–15. doi:10.1007/s00210-024-03318-x.
21. Sivaraj C., D. Pavithra, et al., “Molecular mechanism of action, resistance to antibiotics and modern approaches”: An overview. The Microbe, 100502. 2025. doi:10.1016/j.microb.2025.100502
22. Fleming, Alexander. 1945. “Penicillin’s Finder Assays Its Future.” *New York Times* 26:21.
23. Gencay, Yilmaz Emre, Džiuginta Jasinskytė, Camille Robert, Szabolcs Semsey, Virginia Martínez, Anders Østergaard Petersen, Katja Brunner, Ana de Santiago Torio, Alex Salazar, and Iszabela Cristiana Turcu. 2024. “Engineered Phage with Antibacterial CRISPR–Cas Selectively Reduce E. Coli Burden in Mice.” *Nature Biotechnology* 42(2):265–74.
24. Goodridge, Lawrence D. 2013. “Bacteriophages for Managing Shigella in Various Clinical and Non-Clinical Settings.” *Bacteriophage* 3(1):e25098. doi:10.4161/bact.25098.
25. Gordillo Altamirano, Fernando L., Xenia Kostoulias, Dinesh Subedi, Denis Korneev, Anton Y. Peleg, and Jeremy J. Barr. 2022. “Phage-Antibiotic Combination Is a Superior Treatment against Acinetobacter Baumannii in a Preclinical Study.” *EBioMedicine* 80:104045. doi:10.1016/j.ebiom.2022.104045.
26. d’Herelle, M. F. 1961. “Sur Un Microbe Invisible Antagoniste Des Bacilles Dysentériques.” *Acta Kravsi*.
27. Huang, Kexin, Cao Xiao, Lucas M. Glass, and Jimeng Sun. 2021. “MolTrans: Molecular Interaction Transformer for Drug–Target Interaction Prediction.” *Bioinformatics* 37(6):830–36.
28. Huda, Shamsul, Md Aftab Alam, and Pramod Kumar Sharma. 2020. “Smart Nanocarriers-Based Drug Delivery for Cancer Therapy: An Innovative and Developing Strategy.” *Journal of Drug Delivery Science and Technology* 60:102018. doi:10.1016/j.jddst.2020.102018.
29. Islam, Md. Sharifull, Jie Fan, and Fan Pan. 2023. “The Power of Phages: Revolutionizing Cancer Treatment.” *Frontiers in Oncology* 13:1290296. doi:10.3389/fonc.2023.1290296.
30. Kalidass, Bharathi, Abdul Azeez Nazeer, Malathi Mahalingam, Ramalingam Karthik Raja, and Dinesh Kumar Lakshmanan. 2025. “Exploring the Pharmacokinetic, Toxicity and Anti-Arthritic Activity of Bioactive Polyphenols to Mitigate the HIF-Regulated Angiogenic-Pannus Growth in Rheumatoid Arthritis.” *International Immunopharmacology* 158:114851.
31. Karthik Raja, Ramalingam, Seetharaman Prabu Kumar, Govindasamy Balasubramani, Chellappa Sankaranarayanan, Bo Liu, Selcuk Hazir, and Mathiyazhagan Narayanan. 2025. “An Updated Review on Green Synthesized Nanoparticles to Control Insect Pests.” *Journal of Pest Science* 98(1):31–50. doi:10.1007/s10340-024-01863-1.
32. Kebriaei, Razieh, Susan M. Lehman, Rahi M. Shah, Kyle C. Stamper, Ashlan J. Kunz Coyne, Dana Holger, Amer El Ghali, and Michael J. Rybak. 2023. “Optimization of Phage-Antibiotic Combinations against Staphylococcus Aureus Biofilms.” *Microbiology Spectrum* 11(3):e0491822. doi:10.1128/spectrum.04918-22.
33. R.K. Niranjan Kumar, S. Rajan, et al., “Revolutionizing waste management: Exploring cutting-edge innovations by CRISPR technologies in composting and vermicomposting”. Journal of Environmental Chemical Engineering, 14: 122389. 2026. doi.org/10.1016/j.jece.2026.122389
34. Khambhati, Khushal, Gargi Bhattacharjee, Nisarg Gohil, Gurneet K. Dhanoa, Antonia P. Sagona, Indra Mani, Nhat Le Bui, Dinh-Toi Chu, Janardhan Keshav Karapurkar, Su Hwa Jang, Hee Yong Chung, Rupesh Maurya, Khalid J. Alzahrani, Suresh Ramakrishna, and Vijai Singh. 2023. “Phage Engineering and Phage-assisted CRISPR-Cas Delivery to Combat Multidrug-resistant Pathogens.” *Bioengineering & Translational Medicine* 8(2):e10381. doi:10.1002/btm2.10381.
35. Kim, Paul, Ana M. Sanchez, Taylor J. R. Penke, Hannah H. Tuson, James C. Kime, Robert W. McKee, William L. Slone, Nicholas R. Conley, Lana J. McMillan, Cameron J. Prybol, and Paul M. Garofolo. 2024. “Safety, Pharmacokinetics, and Pharmacodynamics of LBP-EC01, a CRISPR-Cas3-Enhanced Bacteriophage Cocktail, in Uncomplicated Urinary Tract Infections Due to Escherichia Coli (ELIMINATE): The Randomised, Open-Label, First Part of a Two-Part Phase 2 Trial.” *The Lancet. Infectious Diseases* 24(12):1319–32. doi:10.1016/S1473-3099(24)00424-9.
36. Kornienko, Maria, Nikita Kuptsov, Roman Gorodnichev, Dmitry Bespiatykh, Andrei Guliaev, Maria Letarova, Eugene Kulikov, Vladimir Veselovsky, Maya Malakhova, Andrey Letarov, Elena Ilina, and Egor Shitikov. 2020. “Contribution of Podoviridae and Myoviridae Bacteriophages to the Effectiveness of Anti-Staphylococcal Therapeutic Cocktails.” *Scientific Reports* 10:18612. doi:10.1038/s41598-020-75637-x.
37. Kortright, Kaitlyn E., Benjamin K. Chan, Jonathan L. Koff, and Paul E. Turner. 2019. “Phage Therapy: A Renewed Approach to Combat Antibiotic-Resistant Bacteria.” *Cell Host & Microbe* 25(2):219–32.
38. Sivalingam AM, Arjun P. 2024. Cerebellar Roles in Motor and Social Functions and Implications for ASD. Cerebellum, 23(6):2564-2574.

39. Lewis, Jessica M., Joshua Williams, and Antonia P. Sagona. 2024. “Making the Leap from Technique to Treatment — Genetic Engineering Is Paving the Way for More Efficient Phage Therapy.” *Biochemical Society Transactions* 52(3):1373–84. doi:10.1042/BST20231289.
40. Li, Lingli, Mengya Zhou, Ming Yu, Xu Ren, Linzhi Li, Chunjun Shen, Chunping Deng, Yucheng Liu, and Bing Yang. 2024. “Correlation between the Development of Phage Resistance and the Original Antibiotic Resistance of Host Bacteria under the Co-Exposure of Antibiotic and Bacteriophage.” *Environmental Research* 252:118921. doi:10.1016/j.envres.2024.118921.
41. Lu, Timothy K., and James J. Collins. 2007. “Dispersing Biofilms with Engineered Enzymatic Bacteriophage.” *Proceedings of the National Academy of Sciences* 104(27):11197–202. doi:10.1073/pnas.0704624104.
42. Maimaiti, Zulipikaer, Zhuo Li, Chi Xu, Jiying Chen, and Wei Chai. 2022. “Global Trends and Hotspots of Phage Therapy for Bacterial Infection: A Bibliometric Visualized Analysis from 2001 to 2021.” *Frontiers in Microbiology* 13:1067803. doi:10.3389/fmicb.2022.1067803.
43. Mishra, Vaishnavi, Nandkishor Bankar, Yugeshwari Tiwade, and Sarita Ugemuge. 2024. “How Phage Therapy Works, Its Advantages and Disadvantages: Mini Review.” *Journal of Pure & Applied Microbiology* 18(1). https://search.ebscohost.com/login.aspx?direct=true&profile=ehost&scope=site&authtype=crawler&jrnl=09737510&AN=176159669&h=wLi5SyDfShSsS0nRxpu2yV%2BearowwaA8yG2fiKwyjN2xdub19jKVFMcTKwEpa%2F6Q50hSrXgKN9kxBNPJ2An7HQ%3D%3D&crl=c.
44. Murray, Ellen, Lorraine A. Draper, R. Paul Ross, and Colin Hill. 2021. “The Advantages and Challenges of Using Endolysins in a Clinical Setting.” *Viruses* 13(4):680.
45. Niveda, S., OM Fasalu Rahiman, P. K. Sreenadh, and ML Lal Prasanth. 2024. “A Review on the Crisis of Antibiotic Resistance and the Strategies to Combat Resistance.” *Journal of Current Research in Scientific Medicine* 10(2):148–54.
46. Olawade, David B., Oluwaseun Fapohunda, Eghosasere Egbon, Oladipo A. Ebiesuwa, Sunday Oluwadamilola Usman, Alaba O. Faronbi, and Sandra Chinaza Fidelis. 2024. “Phage Therapy: A Targeted Approach to Overcoming Antibiotic Resistance.” *Microbial Pathogenesis* 197:107088. doi:10.1016/j.micpath.2024.107088.
47. Onallah, Hadil, Ronen Hazan, Ran Nir-Paz, Michael J. Brownstein, Joseph R. Fackler, Bri’Anna Horne, Robert Hopkins, Subhendu Basu, Ortal Yerushalmy, and Sivan Alkalay-Oren. 2023. “Refractory Pseudomonas Aeruginosa Infections Treated with Phage PASA16: A Compassionate Use Case Series.” *Med* 4(9):600–611.
48. Petrovic Fabijan, Aleksandra, Ruby C. Y. Lin, Josephine Ho, Susan Maddocks, Nouri L. Ben Zakour, Jonathan R. Iredell, and Westmead Bacteriophage Therapy Team. 2020. “Safety of Bacteriophage Therapy in Severe Staphylococcus Aureus Infection.” *Nature Microbiology* 5(3):465–72. doi:10.1038/s41564-019-0634-z.
49. Pirnay, Jean-Paul, Sarah Djebara, Griet Steurs, Johann Griselain, Christel Cochez, Steven De Soir, Tea Glonti, An Spiessens, Emily Vanden Berghe, and Sabrina Green. 2024. “Personalized Bacteriophage Therapy Outcomes for 100 Consecutive Cases: A Multicentre, Multinational, Retrospective Observational Study.” *Nature Microbiology* 9(6):1434–53.
50. Podlacha, Magdalena, Łukasz Grabowski, Katarzyna Kosznik-Kawśnicka, Karolina Zdrojewska, Małgorzata Stasiłojć, Grzegorz Węgrzyn, and Alicja Węgrzyn. 2021. “Interactions of Bacteriophages with Animal and Human Organisms—Safety Issues in the Light of Phage Therapy.” *International Journal of Molecular Sciences* 22(16):8937. doi:10.3390/ijms22168937.
51. Principi, Nicola, Ettore Silvestri, and Susanna Esposito. 2019. “Advantages and Limitations of Bacteriophages for the Treatment of Bacterial Infections.” *Frontiers in Pharmacology* 10:457104.
52. R. Ramalingam Karthik, Prabu Kumar Seetharaman, Bharathi Kalidass, Siva Ananth, Liu Bo, Chinnaperumal Kamaraj, Harun Cimen, and Selcuk Hazir. 2024. “Biosynthesis of Selenium Nanoparticles Using Cell-Free Extract of Xenorhabdus Cabanillasii GU480990 and Their Potential Mosquito Larvicidal Properties against Yellow Fever Mosquito Aedes Aegypti.” *Journal of Invertebrate Pathology* 203:108045.
53. Roche, Paul A., and Kazuyuki Furuta. 2015. “The Ins and Outs of MHC Class II-Mediated Antigen Processing and Presentation.” *Nature Reviews. Immunology* 15(4):203–16. doi:10.1038/nri3818.
54. Sabur, Abdus, Angkan Khan, B. Borphukan, Abdur Razzak, M. Salimullah, and Muslima Khatun. 2025. “The Unique Capability of Endolysin to Tackle Antibiotic Resistance: Cracking the Barrier.” *Journal of Xenobiotics* 15(1):19.
55. Salam, Md. Abdus, Md. Yusuf Al-Amin, Moushumi Tabassoom Salam, Jogendra Singh Pawar, Naseem Akhter, Ali A. Rabaan, and Mohammed A. A. Alqumber. 2023. “Antimicrobial Resistance: A Growing Serious Threat for Global Public Health.” *Healthcare* 11(13):1946. doi:10.3390/healthcare11131946.
56. Sawa, Teiji, Kiyoshi Moriyama, and Mao Kinoshita. 2024. “Current Status of Bacteriophage Therapy for Severe Bacterial Infections.” *Journal of Intensive Care* 12(1):44. doi:10.1186/s40560-024-00759-7.
57. Sharma, Soumya. 2024. “Armata Completes Phase II Tailwind Study Enrollment in US.” https://www.clinicaltrialsarena.com/news/armata-phase-ii-tailwind-enrollment/.
58. Strathdee, Steffanie A., Graham F. Hatfull, Vivek K. Mutalik, and Robert T. Schooley. 2023. “Phage Therapy: From Biological Mechanisms to Future Directions.” *Cell* 186(1):17–31. doi:10.1016/j.cell.2022.11.017.
59. Arjun P, Rajinikanth V, Mathiyazhagan N. 2025. Harnessing marine macroalgae for bioplastic materials production: a comprehensive review. Discover Materials, 5:172
60. Supina, Brittany SI, and Jonathan J. Dennis. 2025. “The Current Landscape of Phage–Antibiotic Synergistic (PAS) Interactions.” *Antibiotics* 14(6):545.
61. Sweere, Johanna M., Jonas D. Van Belleghem, Heather Ishak, Michelle S. Bach, Medeea Popescu, Vivekananda Sunkari, Gernot Kaber, Robert Manasherob, Gina A. Suh, Xiou Cao, Christiaan R. de Vries, Dung N. Lam, Payton L. Marshall, Maria Birukova, Ethan Katznelson, Daniel V. Lazzareschi, Swathi Balaji, Sundeep G. Keswani, Thomas R. Hawn, Patrick R. Secor, and Paul L. Bollyky. 2019. “Bacteriophage Trigger Antiviral Immunity and Prevent Clearance of Bacterial Infection.” *Science* 363(6434):eaat9691. doi:10.1126/science.aat9691.

62. Tridgett, Matthew, Maria Ababi, Alexander Osgerby, Robert Ramirez Garcia, and Alfonso Jaramillo. 2021. “Engineering Bacteria to Produce Pure Phage-like Particles for Gene Delivery.” *ACS Synthetic Biology* 10(1):107–14. doi:10.1021/acssynbio.0c00467.
63. Twort, F. W. 1915. “AN INVESTIGATION ON THE NATURE OF ULTRA-MICROSCOPIC VIRUSES.” *The Lancet* 186(4814):1241–43. doi:10.1016/S0140-6736(01)20383-3.
64. Uchechukwu, Chidiebere F., and Adedayo Shonekan. 2024. “Current Status of Clinical Trials for Phage Therapy.” *Journal of Medical Microbiology* 73(9):001895. doi:10.1099/jmm.0.001895.
65. Uyttebroek, Saartje, Baixing Chen, Jolien Onsea, Fred Ruythooren, Yves Debaveye, David Devolder, Isabel Spriet, Melissa Depypere, Jeroen Wagemans, Rob Lavigne, Jean-Paul Pirnay, Maya Merabishvili, Paul De Munter, Willy E. Peetermans, Lieven Dupont, Laura Van Gerven, and Willem-Jan Metsemakers. 2022. “Safety and Efficacy of Phage Therapy in Difficult-to-Treat Infections: A Systematic Review.” *The Lancet. Infectious Diseases* 22(8):e208–20. doi:10.1016/S1473-3099(21)00612-5.
66. Van Nieuwenhuyse, Brieuc, Dimitri Van der Linden, Olga Chatzis, Cédric Lood, Jeroen Wagemans, Rob Lavigne, Kaat Schroven, Jan Paeshuyse, Catherine De Magnee, and Etienne Sokal. 2022. “Bacteriophage-Antibiotic Combination Therapy against Extensively Drug-Resistant Pseudomonas Aeruginosa Infection to Allow Liver Transplantation in a Toddler.” *Nature Communications* 13(1):5725.
67. vasundhara. 2023. “Adaptive Phage Begins Subject Dosing in Cystic Fibrosis Therapy Trial.” https://www.clinicaltrialsarena.com/news/adaptive-phage-cystic-fibrosis/.
68. Venkataraman, Srividhya, Mehdi Shahgolzari, Afagh Yavari, and Kathleen Hefferon. 2025. “Bacteriophages as Targeted Therapeutic Vehicles: Challenges and Opportunities.” *Bioengineering* 12(5):469.
69. Wang, Lei, Zehua Wen, Shi-Wei Liu, Lihong Zhang, Cierra Finley, Ho-Jin Lee, and Hua-Jun Shawn Fan. 2024. “Overview of AlphaFold2 and Breakthroughs in Overcoming Its Limitations.” *Computers in Biology and Medicine* 176:108620. doi:10.1016/j.compbiomed.2024.108620.
70. Washizaki, Ayaka, Arata Sakiyama, and Hiroki Ando. 2024. “Phage-Specific Antibodies: Are They a Hurdle for the Success of Phage Therapy?” *Essays in Biochemistry* 68(5):633–44. doi:10.1042/EBC20240024.
71. WHO bacterial priority pathogens list,. 2024. https://www.who.int/publications/i/item/9789240093461.
72. Yosef, Ido, Miriam Manor, Ruth Kiro, and Udi Qimron. 2015. “Temperate and Lytic Bacteriophages Programmed to Sensitize and Kill Antibiotic-Resistant Bacteria.” *Proceedings of the National Academy of Sciences* 112(23):7267–72. doi:10.1073/pnas.1500107112.
73. Sukirtha R., Suguna K., Bharathiraja C., Karthikeyan K., Arjun P., Kumar C., Mysoon M.A.A., Vimal S., Srinivasan P. 2025. Luminescent Biogenic Selenium Nanoparticles From *Indigofera aspalathoides* Vahl ex DC: A Novel Hepatoprotective Strategy for Enhancing Liver Health. Luminescence, 40:e70101.
74. Young, Matthew J., Lesley M. L. Hall, Maya Merabishvilli, Jean-Paul Pirnay, Jason R. Clark, and Joshua D. Jones. 2023. “Phage Therapy for Diabetic Foot Infection: A Case Series.” *Clinical Therapeutics* 45(8):797–801. doi:10.1016/j.clinthera.2023.06.009.
75. Zalewska-Piątek, Beata, and Rafał Piątek. 2021. “Bacteriophages as Potential Tools for Use in Antimicrobial Therapy and Vaccine Development.” *Pharmaceuticals (Basel, Switzerland)* 14(4):331. doi:10.3390/ph1404033