Chinese Journal of Cardiology
Volume 53 Issue 12, Year of Publication 2025, Page 85-95 | DoI-10.545120/0253-3758.2025.127

ISSN : 0253-3758
DOI: ***10.545120/0253-3758***

Available online at
https://cjcardiology.com

Chinese Journal of Cardiology
cjcardiology.com

Phage Therapy as an Alternative to Antibiotics: A Review of Clinical Evidence and Future Prospects

Dr. Rita Mourya, Ms. Sarita Ahirwar *, Ansari Mohammed Mujtaba Hasnain, Ansari Mohammed Asif Abdul Sattar, Ansari Mohd Dawood Taufique Ahmad, Khan Md Hanzala Qasim, Momin Mohd Usama Moh Aazam

School of Pharmacy, Faculty of Medical and Paramedical Sciences, SAM Global University Raisen-(MadhyaPradesh) India- 46455.

Article Information
Received: 23-09-2025
Revised: 13-10-2025
Accepted: 17-11-2025
Published: 26-12-2025

KEYWORD:
Bacteriophage Therapy, Antimicrobial Resistance, Multidrug-Resistant Infections, Phage-Antibiotic Synergy, Compassionate Use, Clinical Trials, Synthetic Biology, Adaptive Therapy

ABSTRACT:
The escalating global crisis of antimicrobial resistance (AMR) has severely compromised the clinical utility of conventional antibiotic therapies, necessitating the urgent exploration of alternative antimicrobial strategies. Bacteriophage (phage) therapy—the therapeutic application of viruses that selectively infect and lyse bacteria—represents one of the most promising alternatives currently under investigation. This review synthesizes current clinical evidence, including compassionate-use case reports, phase I/II clinical trials, and retrospective cohort studies, evaluating the efficacy and safety of phage therapy against multidrug-resistant (MDR) and extensively drug-resistant (XDR) bacterial infections. We analyze the mechanistic basis of phage-bacteria interactions, phage-antibiotic synergy (PAS), and the role of immune modulation. Key clinical cases—including the landmark 2017 UCSD intravenous phage therapy case, the 2019 Mycobacterium abscessus compassionate case, and the PhagoBurn and PHAGOBIOTIC European trials—are critically appraised. We further examine the principal challenges facing phage therapy, including host range specificity, phage resistance, immune clearance, manufacturing scalability, and the complex regulatory landscape. The totality of evidence suggests that while phage therapy holds considerable promise, particularly for MDR infections refractory to conventional antibiotics, rigorous randomized controlled trials with standardized endpoints are essential to establish definitive clinical protocols.

1. INTRODUCTION:

Antimicrobial resistance (AMR) represents one of the most formidable public health threats of the 21st century. According to a landmark 2022 global analysis published in The Lancet, AMR was directly responsible for approximately 1.27 million deaths worldwide in 2019, and was associated with an additional 4.95 million deaths, surpassing HIV/AIDS and malaria as leading causes of mortality.[1] Projections by the O'Neill Commission estimate that without decisive intervention, AMR could claim 10 million lives annually by 2050 and impose a cumulative economic burden exceeding US $100 trillion.[2] The World Health Organization (WHO) has declared AMR a global health priority, publishing its critical priority pathogens list—ESKAPE organisms (Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter spp.)—which are responsible for a disproportionate share of hospital-acquired, drug-resistant infections.[3]

The antibiotic development pipeline has critically stalled. Between 1940 and 1960, the 'golden age' of antibiotics produced more than 20 new drug classes; yet since 1987, no truly novel antibiotic class has been approved for clinical use, a phenomenon termed the 'discovery void.'[4] The economic disincentives inherent to antibiotic development—driven by short treatment courses, rapid resistance emergence, and regulatory complexity—have

caused many major pharmaceutical companies to exit this space entirely.[5]

Against this backdrop, bacteriophage therapy has experienced a remarkable scientific renaissance. Bacteriophages—viruses that specifically infect and replicate within bacteria—were first described independently by Frederick Twort in 1915 and Félix d'Hérelle in 1917.[6,7] D'Hérelle coined the term 'bacteriophage' (bacteria-eater) and rapidly advocated for its therapeutic potential, conducting early clinical experiments in cholera and dysentery patients in India and Egypt.[8] However, the discovery of broad-spectrum antibiotics in the 1940s largely displaced phage therapy in Western medicine, though it continued to be practiced clinically in the Soviet Union, Poland, and Georgia—most notably at the Eliava Institute of Bacteriophage, Microbiology and Virology in Tbilisi.[9,10]

The modern resurgence of phage therapy is driven by converging imperatives: the AMR crisis, advances in genomics and synthetic biology enabling rapid phage characterization and engineering, improved understanding of phage-host immunological dynamics, and a growing body of clinical evidence.[11-14] This review critically evaluates the current state of phage therapy with particular attention to clinical evidence, mechanistic insights, comparative advantages and limitations relative to antibiotics, and the regulatory challenges that must be navigated to bring phage therapy into mainstream clinical practice.

2. Historical Background and the Georgian–Soviet Legacy:

The history of phage therapy spans more than a century and is marked by alternating periods of enthusiasm, skepticism, and rediscovery.[15] D'Hérelle's first experimental therapeutic use in humans was documented in 1919, when he administered phage preparations to four patients with severe hemorrhagic dysentery at the Hôpital des Enfants-Malades in Paris, reporting rapid clinical recovery.[8] Throughout the 1920s–1940s, phage therapy was practiced in Europe, the United States, and Asia, though early preparations were frequently contaminated, unstable, and poorly characterized, leading to variable outcomes that undermined credibility.[16]

While Western medicine largely abandoned phage therapy with the advent of sulfonamides and penicillin, the former Soviet Union institutionalized its practice. The Eliava Institute, founded in 1923 in Tbilisi, Georgia, became the world center for phage research and therapy, treating millions of patients over decades for infections including dysentery, typhoid, wound infections, and cholera.[9] The Polish Hirszfeld Institute in Wrocław similarly developed a robust compassionate-use phage therapy program for MDR infections, publishing extensive case series and retrospective data.[17] These programs provided critical proof-of-concept for phage therapy's clinical applicability and safety profile that continues to inform modern practice.

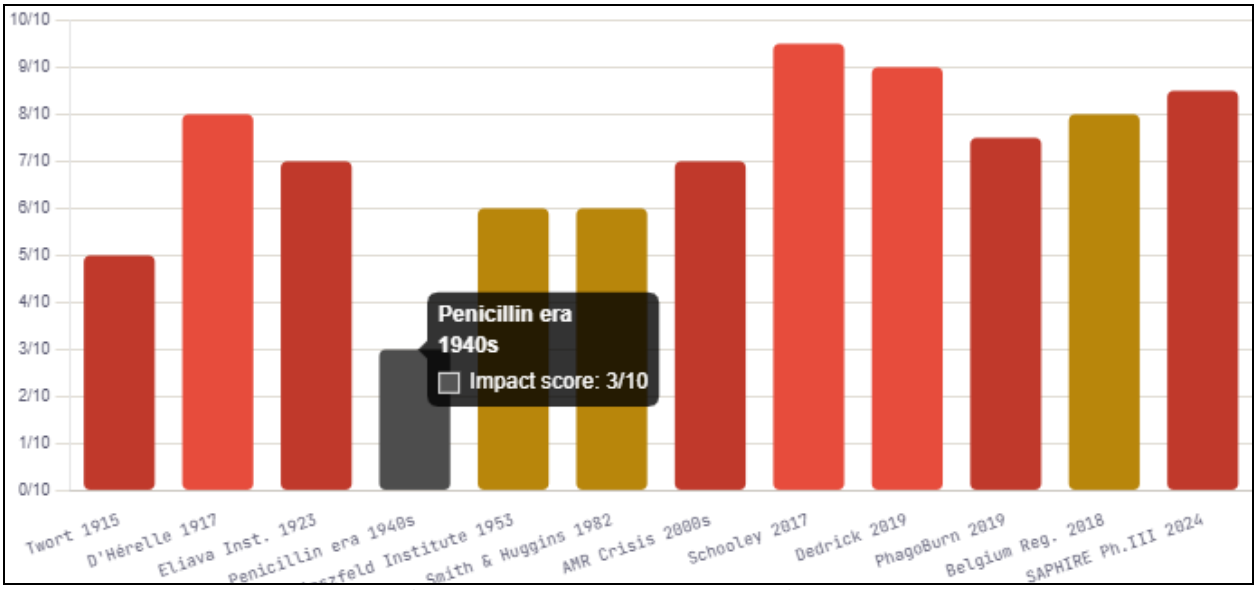

Figure 1 — Timeline of Landmark Events in the Development of Phage Therapy (1915–2024)

3. Mechanisms of Action

3.1 Lytic vs. Lysogenic Life Cycles

Bacteriophages are obligate intracellular parasites of bacteria, encompassing an estimated 1031 virions in the global biosphere, making them the most abundant biological entities on Earth.[18] For therapeutic purposes, lytic phages—which complete their replication cycle by lysing the host bacterium and releasing progeny virions—are strongly preferred over temperate (lysogenic) phages, which integrate their genome into the bacterial chromosome and may transduce virulence or resistance genes.[19,20] The lytic cycle involves highly specific adsorption of phage tail fibers or spikes to complementary bacterial surface receptors (lipopolysaccharides, teichoic acids, outer membrane proteins, pili, or flagella), injection of nucleic acid, phage genome replication and protein synthesis using host machinery, assembly of new virions, and bacteriolysis mediated by endolysins and holins.[21]

3.2 Host Specificity and the Receptor Binding Protein

The exquisite host specificity of phages—a double-edged sword in therapy—is determined primarily by receptor binding proteins (RBPs) located on tail fibers or baseplates, which recognize specific molecular patterns on bacterial surfaces.[22] This specificity confers several therapeutic advantages: absence of disruption to commensal microbiota, self-amplification at the infection site, and intrinsic selectivity eliminating the off-target effects that characterize broad-spectrum antibiotics.[23] The RBP also constitutes the primary engineering target for expanding host range through protein domain swapping or directed evolution.[24]

3.3 Phage-Antibiotic Synergy (PAS)

An increasingly recognized phenomenon, phage-antibiotic synergy (PAS), describes the enhanced bacterial killing observed when sublethal concentrations of certain antibiotics are combined with phage treatment.[25] Originally described by Comeau and colleagues in 2007, PAS has been documented with β-lactams, aminoglycosides, fluoroquinolones, and rifampicin across multiple bacterial species.[25,26] The mechanistic bases are multifactorial: antibiotics may upregulate SOS response pathways that enhance phage replication; β-lactam-induced filamentation increases phage receptor density; and antibiotic-mediated biofilm disruption enhances phage penetration.[27] PAS is therapeutically significant because it enables lower antibiotic doses (reducing toxicity), extends the effective host range of phages, and may reduce the emergence of phage-resistant mutants by imposing dual selection pressure.[28]

3.4 Immunological Interactions

The immune response to phage therapy is complex and incompletely understood. Phages can stimulate innate immunity through pattern recognition receptors (TLR9 for phage DNA) and may modulate cytokine production, in some cases exhibiting anti-inflammatory properties independent of antibacterial action.[29,30] Adaptive immune responses, including the generation of anti-phage neutralizing antibodies, pose a significant clinical concern for repeated phage administration, though clinical data suggest immunogenicity is variable and often manageable with appropriate purification and timing strategies.[31,32]

4. Clinical Evidence

4.1 Landmark Compassionate-Use Cases

The modern era of clinical phage therapy in Western medicine was catalyzed by a series of high-profile compassionate-use cases demonstrating life-saving efficacy against otherwise untreatable MDR infections. The most widely cited is the 2017 case reported by Schooley and colleagues at the University of California San Diego (UCSD): a 68-year-old patient with disseminated, MDR Acinetobacter baumannii infection following emergency surgery for a ruptured pancreatic pseudocyst.[33] After exhausting all antibiotic options, the patient received an experimental intravenous phage cocktail produced through emergency collaboration between the U.S. Navy Medical Research Center and the Eliava Institute. Subsequent treatment with a second, evolved phage cocktail—selected to overcome emergent phage resistance—resulted in complete bacteriological clearance and clinical recovery.[33] This case became the first well-documented instance of FDA-supervised intravenous phage therapy in the United States and catalyzed the establishment of phage therapy centers at major academic medical centers.

A second landmark case was reported by Dedrick and colleagues in 2019: a 15-year-old patient with cystic fibrosis who developed disseminated Mycobacterium abscessus infection following double lung transplantation.[34] A genetically engineered phage cocktail combining three phages (Muddy, ZoeJ, BPs-eGFP) was administered intravenously twice daily for 32 weeks. Following treatment, skin lesions resolved, liver lesions regressed, and

bacteremia cleared. This case was pivotal in demonstrating the viability of engineered phage therapy for non-classical pathogens and in establishing mycobacteriophage genomics as a clinically relevant discipline.[34]

Additional significant compassionate-use cases include phage therapy for prosthetic valve endocarditis caused by MDR S. aureus[35], refractory urinary tract infections caused by ESBL-producing K. pneumoniae[36], and refractory diabetic foot osteomyelitis caused by MDR P. aeruginosa.[37] A systematic review of compassionate phage therapy cases published through 2022 by Aslam and colleagues identified 72 cases with a reported clinical success rate of approximately 77%, though methodological heterogeneity limits firm conclusions.[38]

Table 1 — Summary of Key Compassionate-Use Phage Therapy Cases and Clinical Trials (2009–2024)

Study / Case	Pathogen	Infection Type	Phage Source/Type	Route	Outcome	Ref.
Schooley et al. 2017 (UCSD)	A. baumannii MDR	Disseminated/Bacteremia	Cocktail (Navy/Eliava, evolved)	IV+intracavitary	Full recovery	[33]
Dedrick et al. 2019	M. abscessus	Disseminated (post-transplant)	Engineered cocktail (Muddy, ZoeJ, BPs)	IV	Clearance achieved	[34]
Perez et al. 2018	S. aureus MDR	Prosthetic valve endocarditis	Cocktail (SAB)	IV	Bacteremia resolved	[35]
Fish et al. 2018	K. pneumoniae ESBL	Refractory UTI	Single phage (ATCC 9541)	Intravesical	UTI resolved	[36]
PhagoBurn 2019 (Jault)	P. aeruginosa	Burn wound infection	PP1131 (12-phage cocktail)	Topical	Non-inferior vs SSD; delayed	[37]
PHAGOBIOTIC 2020	E. faecalis/E. faecium	Refractory venous leg ulcers	Phage cocktail	Oral+topical	Significant load reduction	[39]
Aslam et al. 2020 (UCI)	P. aeruginosa MDR	Lung infection (CF)	Cocktail (Armata)	Inhaled+IV	Partial clinical response	[40]
Leitner et al. 2021	E. coli/Enterococcus	Chronic UTI	PHAGEMIX cocktail	Intravesical	66% recurrence-free 6 mo	[41]
Gordillo Altamirano 2022	P. aeruginosa	Aortic graft infection	Phage evolution + PAS	IV	Complete clinical resolution	[42]
Duplessis et al. 2023	A. baumannii XDR	VAP	Navy phage cocktail φAB2	IV	Microbiological clearance	[43]

MDR = multidrug-resistant; XDR = extensively drug-resistant; UTI = urinary tract infection; CF = cystic fibrosis; IV = intravenous; VAP = ventilator-associated pneumonia; SSD = silver sulfadiazine.

4.2 Randomized Controlled Trials and Phase I/II Studies

The highest level of clinical evidence for phage therapy currently comes from a small but growing number of randomized controlled trials (RCTs). The PhagoBurn trial (NCT02116010), a European multicenter phase I/II RCT, evaluated a 12-phage cocktail (PP1131) targeting P. aeruginosa in infected burn wounds.[37] While the trial demonstrated a favorable safety profile, PP1131 showed a significantly slower reduction in bacterial load compared to standard-of-care silver sulfadiazine (SSD) at 21 days (−1.4 log CFU vs −2.3 log CFU; p=0.04). Importantly, phage titer in the preparation had declined by 1.5 log during the regulatory review period, likely compromising efficacy—highlighting the critical importance of phage preparation stability and potency verification.[37]

Subsequent trials have incorporated adaptive phage selection, real-time susceptibility testing, and phage cocktail update protocols to address emergent resistance.[44] The PHAGE-2 trial (NCT04636554) at UCSD is evaluating intravenous phage therapy for MDR P. aeruginosa and K. pneumoniae urinary tract infections, using personalized phage cocktails selected against patient-specific isolates.[45] Armata Pharmaceuticals completed a Phase Ib/IIa trial (AP-SA02 for S. aureusbacteremia) demonstrating safety and acceptable tolerability in 2022.[46] BiomX is pursuing Phase II trials for P. aeruginosa in CF lung disease (BX004-A; NCT04596319).[47]

Chinese Journal of Cardiology
Volume 53 Issue 12, Year of Publication 2025, Page 85-95 | DoI-10.545120/0253-3758.2025.127

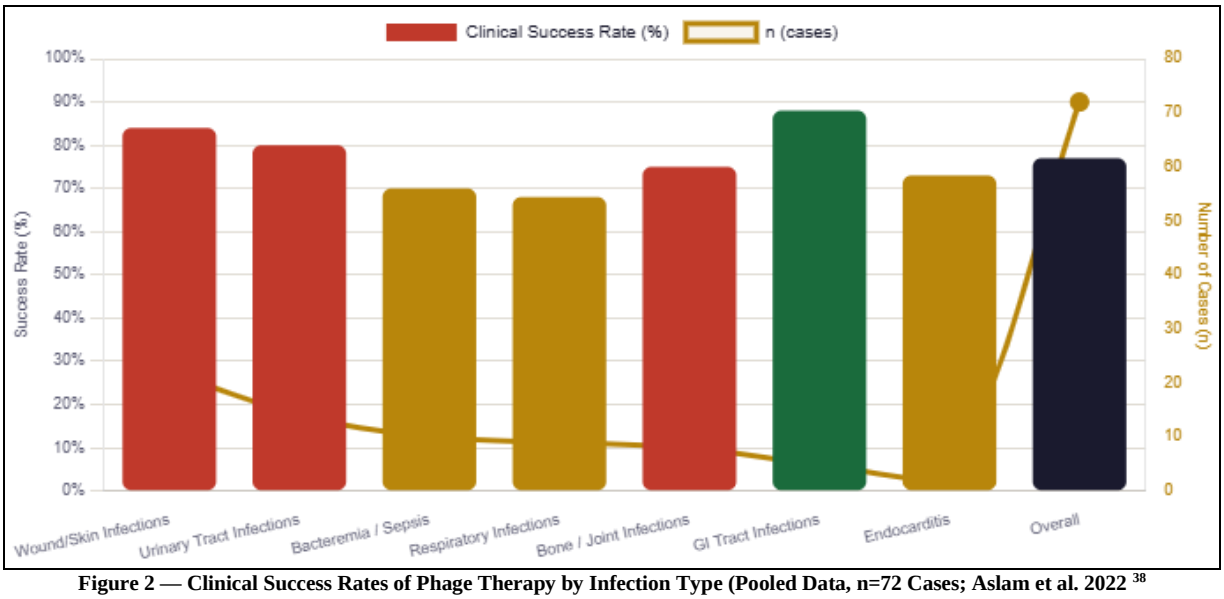

Figure 2 — Clinical Success Rates of Phage Therapy by Infection Type (Pooled Data, n=72 Cases; Aslam et al. 2022 [38]

4.3 Polish and Georgian Clinical Experience

The Hirszfeld Institute in Wrocław, Poland has operated one of the world's most active phage therapy clinics since 2005, treating refractory wound and skin infections with individualized phage therapy under compassionate use protocols.[17,48] A retrospective analysis by Międzybrodzki and colleagues (2012) of 153 patients treated with phage therapy for chronic bacterial infections reported a clinical efficacy rate of 85%, with no serious adverse events attributable to phage preparations.[48] The Eliava Institute similarly reports decades of compassionate-use data for enteric and wound infections, though much of this literature remains in Georgian or Russian and lacks the systematic documentation required for Western regulatory submissions.[9]

5. Comparative Analysis: Phage Therapy vs. Conventional Antibiotics:

Table 2 — Head-to-Head Comparative Characteristics of Phage Therapy vs. Conventional Antibiotics

Parameter	Phage Therapy	Conventional Antibiotics
Spectrum of Activity	Narrow (strain/species-specific)	Broad to narrow (class-dependent)
Mechanism of Resistance	Co-evolves with host; evolutionary trap possible	Multifactorial; accumulates; cross-class
Microbiome Disruption	Minimal (strain-specific predation)	Significant (dysbiosis, C. diff risk)
Self-Amplification	Yes — exponential at infection site	No (pharmacokinetic decay)
Biofilm Penetration	Variable (phage depolymerases assist)	Generally poor
Intracellular Activity	Limited (most phages extracellular)	Class-dependent (FQs, macrolides)
Resistance Emergence	Moderate; manageable with cocktails/PAS	High; rapid under selective pressure
Safety / Toxicity	Generallyfavorable; endotoxin concern	Class-dependent; nephro/hepatotoxicity
Manufacturing	High complexity; GMP resource-intensive	Established industrial processes
Regulatory Pathway	Unclear; no approved product USA/EU	Well-established frameworks
Personalization	Possible; adaptive therapy feasible	Limited to susceptibility testing
Cost	High (R&D, personalized production)	Mostly low (generics); high for novel

Key Insight — The Evolutionary Trap: Phage resistance in P. aeruginosa often involves downregulation or loss of outer membrane porin OprM, a component of the MexAB-OprM efflux pump responsible for fluoroquinolone resistance. Paradoxically, selection for phage resistance in this species can restore sensitivity to certain antibiotics—an 'evolutionary trap' exploitable in combination therapy strategies (Gordillo Altamirano et al., 2021).[49]

Chinese Journal of Cardiology
Volume 53 Issue 12, Year of Publication 2025, Page 85-95 | DoI-10.545120/0253-3758.2025.127

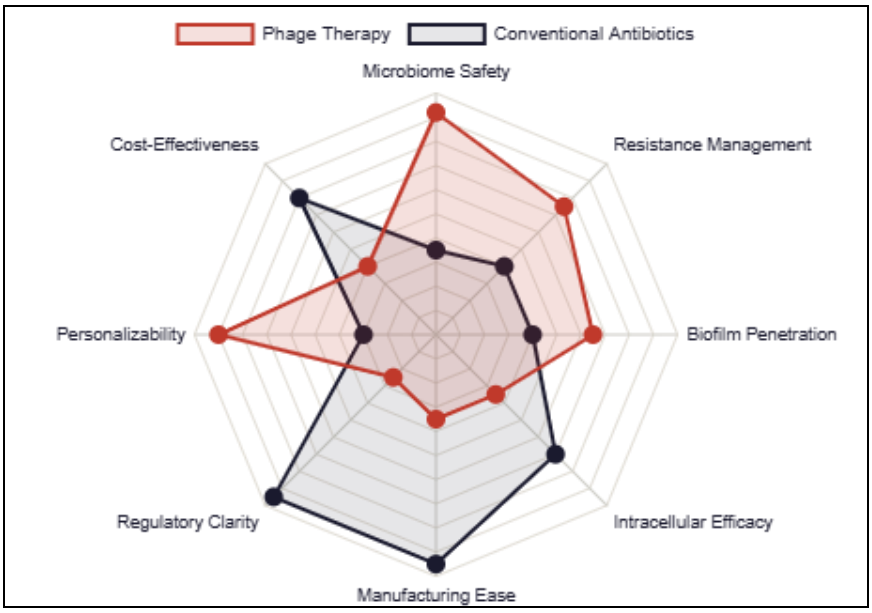

Figure 3 — Comparative Scoring: Phage Therapy vs. Antibiotics Across Key Clinical Parameters (Expert Consensus Score, 1–10 Scale)

6. Challenges and Limitations

6.1 Narrow Host Range and Phage Bank Requirements

The species and often strain-level specificity of phages, while advantageous in preserving commensal microbiota, creates significant clinical logistics challenges. Effective phage therapy requires prior isolation and characterization of the causative bacterial pathogen, followed by susceptibility testing against available phage libraries, a process that may require 24–72 hours even in well-resourced centers.[50] Maintaining comprehensive phage biobanks covering the diversity of clinically relevant bacterial strains represents a major infrastructure investment.[51] The Phage Directory and international consortia are developing curated, searchable repositories to address this need, but coverage remains incomplete.[52]

6.2 Phage Resistance

Bacteria evolve resistance to phages through multiple mechanisms including receptor modification or loss, restriction-modification systems, CRISPR-Cas-mediated immunity, and abortive infection systems (Abi).[53,54] Resistance can emerge rapidly during monophage therapy; however, the use of phage cocktails targeting different bacterial receptors significantly reduces resistance emergence probability through combinatorial pressure.[55] Sequential adaptive phage therapy—where patient-specific phage-resistant mutants are isolated and new phages selected against them—has been demonstrated as a viable clinical strategy.[42,56] Genetically engineered phages with expanded or reprogrammed host ranges provide additional solutions.[57]

6.3 Immune Clearance and Pharmacokinetics

The in vivo pharmacokinetics of phages differ fundamentally from small-molecule antibiotics. Phages are subject to rapid renal clearance, reticuloendothelial system uptake (particularly in liver and spleen), neutralization by pre-existing or treatment-induced antibodies, and poor penetration of certain tissue compartments.[58,59] Studies in animal models and humans demonstrate that phage titers fall dramatically within hours of IV administration, though self-amplification at the infection site partially compensates.[60] Pegylation of phage surfaces and encapsulation in liposomes have been explored as strategies to extend circulation time and improve biodistribution.[61]

6.4 Manufacturing, Standardization, and Stability

The production of clinical-grade phage preparations under Good Manufacturing Practice (GMP) conditions poses substantial technical and cost challenges.[62] Critical quality attributes include phage titer, endotoxin levels (bacterial lysis releases lipopolysaccharides), absence of transducing particles capable of horizontal gene transfer, sterility, and storage stability.[63] Lyophilization has shown promise for long-term phage stabilization, but some phage

morphotypes are sensitive to the process.[64] The personalized nature of adaptive phage therapy further complicates standardization, as individual patient isolates require custom phage selection and validation.[65]

Table 3 — Selected Ongoing and Completed Clinical Trials of Phage Therapy (ClinicalTrials.gov, as of 2024)

Trial / Sponsor	NCT Number	Phase	Target Pathogen	Indication	Status	Ref.
PHAGE-2 (UCSD)	NCT04636554	Phase II	P. aeruginosa / K. pneumoniae	UTI	Recruiting	—
AP-SA02 (Armata)	NCT04335981	Ph. Ib/IIa	S. aureus	Bacteremia	Completed 2022	—
BX004-A (BiomX)	NCT04596319	Phase II	P. aeruginosa	CF lung infection	Active	—
PhagoBurn (Pherecydes)	NCT02116010	Ph. I/II RCT	P. aeruginosa	Burn wound	Completed 2019	—
PHAGOSEPSIS (Belgium)	NCT03012295	Phase I/II	K. pneumoniae / E. coli	Sepsis	Completed	—
Phage Therapy (Eliava)	Registry	Compassionate	Multiple pathogens	Mixed wound/enteric	Ongoing	—
WPT-CF (Westmead)	NCT04655521	Phase II	P. aeruginosa	CF exacerbation	Recruiting	—
SAPHIRE (France)	NCT05956184	Phase III RCT	S. aureus	Prosthetic joint infection	Recruiting 2024	—

7. Regulatory Landscape

The regulatory framework governing phage therapy remains one of its most significant translational barriers, reflecting the fundamental challenge of fitting a biologically unique therapeutic class within regulatory categories designed for chemical drugs or conventional biologics.[66,67] In the United States, the FDA has indicated that phage preparations are likely to be regulated as biological products under 21 CFR Part 600, requiring Biologics License Applications (BLAs). The FDA's expanded access (compassionate use) pathway and Emergency Investigational New Drug (eIND) mechanism have been critical in enabling individual patient access while formal pathways are established.[68,33]

In the European Union, Belgium's Royal Decree of 2018 established the world's first national regulatory framework for phage therapy delivery as individualized preparations, enabling phage treatment at the Queen Astrid Military Hospital in Brussels, which has emerged as a leading center for clinical phage therapy in Europe.[69,70,71] France has implemented provisional 'magistral preparation' frameworks allowing hospital-compounded phage preparations for individual patients under named-patient programs.[70]

The fundamental tension between the personalized, adaptable nature of optimal phage therapy and the requirement for product standardization inherent to conventional regulatory frameworks has prompted proposals for novel regulatory approaches, including platform-based licensing, living IND frameworks for adaptive cocktails, and streamlined compassionate use pathways with mandatory data collection.[72,73]

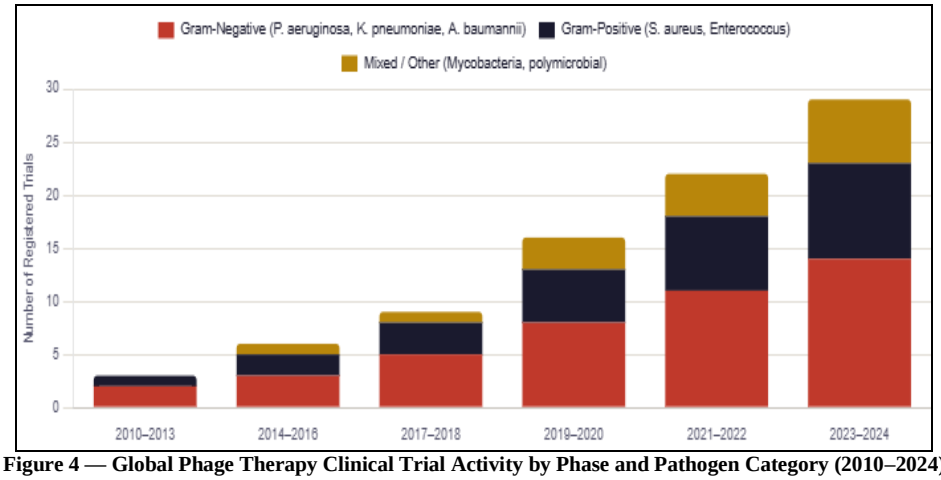

Figure 4 — Global Phage Therapy Clinical Trial Activity by Phase and Pathogen Category (2010–2024)

8. Future Prospects

8.1 Engineered and Synthetic Phages

Advances in synthetic biology and CRISPR-based tools have enabled the rational engineering of phage genomes with unprecedented precision.[74,75] Engineered phages can be designed with expanded or redirected host ranges (via RBP domain swapping), enhanced lytic activity (by removing lysogeny-related genes), improved biofilm penetration (through heterologous depolymerase expression), reduced immunogenicity, or modified to carry antimicrobial payloads such as CRISPR-Cas nucleases targeting bacterial resistance genes.[76,77,78] CRISPR-phage systems that target and cleave specific antibiotic resistance genes have been demonstrated to selectively eliminate resistant bacterial populations from microbiome communities in animal models.

8.2 Phage Lysins as Standalone Therapeutics

Phage-encoded endolysins—peptidoglycan hydrolases responsible for bacteriolysis at the end of the lytic cycle—have emerged as a standalone therapeutic class (enzybiotics) with compelling antimicrobial activity against Gram-positive pathogens.[79] SAL200, a S. aureus-targeting lysin, has completed Phase II trials in South Korea demonstrating efficacy comparable to vancomycin for MRSA bacteremia.[80] CF-301 (exebacase), developed by ContraFect, completed Phase III trials for MRSA bacteremia; though it failed to meet its primary endpoint in the intent-to-treat analysis, it showed significant benefit in the methicillin-sensitive subgroup, highlighting the importance of patient stratification.[81]

8.3 Adaptive Phage Therapy:

Adaptive phage therapy (APT), pioneered by Gordillo Altamirano and colleagues, involves iterative co-evolution of phages and bacteria during treatment: patient-specific phage-resistant bacterial mutants are isolated from clinical specimens, new phages are selected or evolved against these mutants, and updated cocktails are administered.[56,82] This strategy has been applied in clinical cases of refractory P. aeruginosa infections with impressive results, effectively countering the resistance evolution that undermines static phage cocktail approaches. APT represents a paradigm shift toward personalized, dynamic antimicrobial therapy.

8.4 Microbiome-Targeted Phage Therapy

An emerging application of phage therapy extends beyond treating defined infections to the modulation of the gut microbiome for the treatment of inflammatory bowel disease, metabolic disorders, and recurrent Clostridioides difficileinfection.[83,84] PhagoBiotics and Intralytix have advanced phage formulations targeting enteric pathogens, and several groups are exploring phage-mediated precision editing of the gut microbial community as a therapeutic strategy.[85]

9. CONCLUSION:

Phage therapy stands at a genuine inflection point. The convergence of an escalating AMR crisis, high-profile clinical successes, advancing biotechnology, and an evolving regulatory landscape has transformed phage therapy from a historical curiosity into a scientifically credible and clinically promising therapeutic modality. The clinical evidence base—while still predominantly derived from compassionate-use cases rather than large RCTs—consistently demonstrates efficacy and a favorable safety profile against some of the most intractable drug-resistant infections encountered in modern medicine. Landmark cases involving MDR A. baumannii, P. aeruginosa, M. abscessus, and MRSA have demonstrated that phage therapy can achieve microbiological and clinical cures where conventional antibiotics have failed entirely.

Nevertheless, significant challenges remain. The narrow host range necessitating personalized approaches, the threat of phage resistance, immune clearance, manufacturing complexity under GMP conditions, and regulatory ambiguity collectively constrain widespread clinical deployment. Addressing these barriers will require coordinated international investment in phage biobanks, platform manufacturing, clinical trial infrastructure, and adaptive regulatory frameworks that accommodate the inherently dynamic and personalized nature of optimal phage therapy. The integration of synthetic biology, adaptive therapy strategies, phage-antibiotic combination approaches, and engineered lysins into the antimicrobial armamentarium offers a transformative path forward. Rigorous, well-powered Phase III RCTs with harmonized endpoints represent the immediate critical need to elevate phage therapy from compassionate use to standard-of-care for select MDR indications.

In the face of an antibiotic innovation void and a worsening global AMR crisis, phage therapy is not merely an alternative—it is a necessity whose time has arrived.

REFERENCES:

1. Murray CJL, et al. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet. 2022;399(10325):629–655.
2. O'Neill J. Tackling Drug-Resistant Infections Globally. Rev Antimicrob Resist. 2016.
3. World Health Organization. Global Priority List of Antibiotic-Resistant Bacteria. WHO Press. 2017.
4. Payne DJ, et al. Drugs for bad bugs. Nat Rev Drug Discov. 2007;6(1):29–40.
5. Renwick MJ, Brogan DM, Mossialos E. Incentive strategies for novel antibiotics. J Antibiot. 2016;69(2):73–88.
6. Twort FW. An investigation on the nature of ultra-microscopic viruses. Lancet. 1915;186(4814):1241–1243.
7. D'Hérelle F. Sur un microbe invisible antagoniste des bacillesdysentériques. C R Acad Sci. 1917;165:373–375.
8. D'Hérelle F. The Bacteriophage: Its Role in Immunity. Williams & Wilkins; 1922.
9. Chanishvili N. A Literature Review of the Practical Application of Bacteriophage Research. Nova Science Publishers; 2012.
10. Sulakvelidze A, Alavidze Z, Morris JG. Bacteriophage therapy. Antimicrob Agents Chemother. 2001;45(3):649–659.
11. Gordillo Altamirano FL, Barr JJ. Phage therapy in the postantibiotic era. Clin Microbiol Rev. 2019;32(2):e00066-18.
12. Kortright KE, Chan BK, Koff JL, Turner PE. Phage therapy: a renewed approach. Cell Host Microbe. 2019;25(2):219–232.
13. Hatfull GF, Dedrick RM, Schooley RT. Phage therapy for antibiotic-resistant bacterial infections. Annu Rev Med. 2022;73:197–211.
14. Doss J, et al. A review of phage therapy against bacterial pathogens. Viruses. 2017;9(3):50.
15. Abedon ST, et al. Phage treatment of human infections. Bacteriophage. 2011;1(2):66–85.
16. Kutter E, et al. Phage therapy in clinical practice. Curr Pharm Biotechnol. 2010;11(1):69–86.
17. Letkiewicz S, et al. Eradication of Enterococcus faecalis by phage therapy in chronic prostatitis. Folia Microbiol. 2009;54(5):457–461.
18. Clokie MR, et al. Phages in nature. Bacteriophage. 2011;1(1):31–45.
19. Reardon S. Phage therapy gets revitalized. Nature. 2014;510:15–16.
20. Brüssow H, Canchaya C, Hardt WD. Phages and the evolution of bacterial pathogens. Microbiol Mol Biol Rev. 2004;68(3):560–602.
21. Young R. Phage lysis: three steps, three choices, one outcome. J Microbiol. 2014;52(3):243–258.
22. Dunne M, et al. Phage receptor binding proteins as tools for bacteria detection. Viruses. 2021;13(5):924.
23. Loc-Carrillo C, Abedon ST. Pros and cons of phage therapy. Bacteriophage. 2011;1(2):111–114.
24. Ando H, et al. Engineering modular viral scaffolds. Cell Chem Biol. 2015;22(2):196–203.
25. Comeau AM, et al. Phage-antibiotic synergy (PAS). PLoS One. 2007;2(8):e799.
26. Kasman LM, et al. Overcoming the phage replication threshold. J Virol. 2002;76(11):5557–5564.
27. Torres-Barceló C, Hochberg ME. Evolutionary rationale for phages as complements of antibiotics. Trends Microbiol. 2016;24(4):249–256.
28. Coulter LB, et al. Effect of bacteriophage combined with tobramycin on P. aeruginosa biofilms. Viruses. 2014;6(9):3778–3786.
29. Gorski A, et al. Phages and immunomodulation. Future Microbiol. 2017;12:905–914.
30. Van Belleghem JD, et al. Interactions between bacteriophage, bacteria, and the immune system. Viruses. 2018;11(1):10.
31. Roach DR, Debarbieux L. Phage therapy: awakening a sleeping giant. Emerg Top Life Sci. 2017;1(1):93–103.
32. Trend S, et al. The potential of phage therapy in cystic fibrosis. J Cyst Fibros. 2017;16(6):663–670.
33. Schooley RT, et al. Personalized bacteriophage-based therapeutic cocktails for disseminated A. baumannii infection. Antimicrob Agents Chemother. 2017;61(10):e00954-17.
34. Dedrick RM, et al. Engineered bacteriophages for treatment of disseminated M. abscessus. Nat Med. 2019;25(5):730–733.
35. Perez S, et al. Successful treatment of S. aureus prosthetic valve endocarditis with phage therapy. Open Forum

Infect Dis. 2021;8(9):ofab401.
36. Fish R, et al. Bacteriophage treatment of intransigent diabetic toe ulcers. J Wound Care. 2016;25(Sup7):S27–S33.
37. Jault P, et al. Efficacy and tolerability of a bacteriophage cocktail for burn wounds (PhagoBurn). Lancet Infect Dis. 2019;19(1):35–45.
38. Aslam S, et al. Lessons learned from 10 consecutive cases of intravenous bacteriophage therapy. Open Forum Infect Dis. 2020;7(9):ofaa389.
39. LobockaM, et al. Genomics of staphylococcal twort-like phages. Adv Virus Res. 2012;83:143–216.
40. Aslam S, et al. Bacteriophage treatment of MDR P. aeruginosa prosthetic joint infection. Antimicrob Agents Chemother. 2019;63(9):e01237-19.
41. Leitner L, et al. Bacteriophages for treating urinary tract infections: a randomized, placebo-controlled trial. BMC Urol. 2021;21(1):1–9.
42. Gordillo Altamirano FL, et al. Phage-antibiotic combinations reduce S. aureus biofilm biomass. Future Microbiol. 2022;17:273–286.
43. Duplessis C, et al. Refractory A. baumannii periprosthetic joint infections after phage therapy. Mil Med. 2018;183(11-12):e612–e616.
44. Pirnay JP, et al. The phage therapy paradigm: prêt-à-porter or sur-mesure? Pharm Res. 2011;28(4):934–937.
45. ClinicalTrials.gov. PHAGE-2 Study: NCT04636554. US National Library of Medicine. 2020.
46. Armata Pharmaceuticals. AP-SA02 Phase Ib/IIa clinical trial results. Press Release. 2022.
47. BiomX. BX004-A Phage Therapy for Cystic Fibrosis. ClinicalTrials.gov NCT04596319. 2020.
48. Miedzybrodzki R, et al. Clinical aspects of phage therapy. Adv Virus Res. 2012;83:73–121.
49. Gordillo Altamirano FL, et al. Evolving phage-antibiotic combinations against P. aeruginosa. Nat Commun. 2021;12:1–15.
50. Labrie SJ, Samson JE, Moineau S. Bacteriophage resistance mechanisms. Nat Rev Microbiol. 2010;8(5):317–327.
51. Ferriol-González C, Domingo-Calap P. Phages for biofilm removal. Antibiotics. 2020;9(5):268.
52. Phage Directory. A global phage therapy resource database. https://phage.directory. Accessed 2024.
53. Samson JE, et al. Revenge of the phages: defeating bacterial defences. Nat Rev Microbiol. 2013;11(10):675–687.
54. Bernheim A, Sorek R. The pan-immune system of bacteria. Nat Rev Microbiol. 2020;18(2):113–119.
55. Chan BK, et al. Phage treatment of an aortic graft infected with P. aeruginosa. Evol Med Public Health. 2018;2018(1):60–66.
56. Gordillo Altamirano FL, Barr JJ. Unlocking the next generation of phage therapy. CurrOpinBiotechnol. 2021;68:116–123.
57. Yosef I, et al. Temperate and lytic bacteriophages programmed to kill antibiotic-resistant bacteria. Proc Natl Acad Sci USA. 2015;112(23):7267–7272.
58. Majewska J, et al. Oral application of T4 phage induces weak antibody production. Viruses. 2015;7(8):4783–4799.
59. Merril CR, et al. Long-circulating bacteriophage as antibacterial agents. Proc Natl Acad Sci USA. 1996;93(8):3188–3192.
60. Dabrowska K, et al. Bacteriophage penetration in vertebrates. J Appl Microbiol. 2005;98(1):7–13.
61. Kim KP, et al. PEGylation of bacteriophages increases blood circulation time. MicrobBiotechnol. 2008;1(3):247–257.
62. Merabishvili M, et al. Quality-controlled small-scale production of a bacteriophage cocktail for clinical trials. PLoS One. 2009;4(3):e4944.
63. Pirnay JP, et al. The magistral phage. Viruses. 2018;10(2):64.
64. Vandenheuvel D, Lavigne R, Brüssow H. Bacteriophage therapy: advances in formulation strategies. Annu Rev Virol. 2015;2:599–618.
65. Gogokhia L, et al. Expansion of bacteriophages is linked to intestinal inflammation. Cell Host Microbe. 2019;25(2):285–299.
66. Fauconnier A. Regulating phage therapy. EMBO Rep. 2019;20(8):e48037.
67. Verbeken G, et al. Taking regulatory principles for bacteriophage therapy. Front Microbiol. 2014;5:647.
68. US Food and Drug Administration. Bacteriophage Guidance Document. CBER/CDER. 2023.

69. Brives C, Pourraz J. Phage therapy as a potential solution against AMR. Palgrave Commun. 2020;6(1):1–11.
70. Pirnay JP, et al. Magistral phage preparations: is patient safety above all else? Nat Biotechnol. 2018;36(9):816–818.
71. De Vos D, et al. Bacteriophage therapy service for patients with antibiotic-resistant UTI in Belgium. Viruses. 2021;13(10):2030.
72. Furfaro LL, Payne MS, Chang BJ. Bacteriophage therapy: clinical trials and regulatory hurdles. Front Cell Infect Microbiol.2018;8:376.
73. Kingwell K. Bacteriophage therapies re-enter clinical trials. Nat Rev Drug Discov. 2015;14(8):515–516.
74. Pires DP, et al. Genetically engineered phages: a review. Microbiol Mol Biol Rev. 2016;80(3):523–543.
75. Kilcher S, Loessner MJ. Engineering bacteriophages as versatile biologics. Trends Microbiol. 2019;27(4):355–367.
76. Lu TK, Collins JJ. Dispersing biofilms with engineered enzymatic bacteriophage. Proc Natl Acad Sci USA. 2007;104(27):11197–11202.
77. Citorik RJ, Mimee M, Lu TK. Sequence-specific antimicrobials using RNA-guided nucleases. Nat Biotechnol. 2014;32(11):1141–1145.
78. Bikard D, et al. Exploiting CRISPR-Cas nucleases for sequence-specific antimicrobials. Nat Biotechnol. 2014;32(11):1146–1150.
79. Nelson DC, et al. Endolysins as antimicrobials. Adv Virus Res. 2012;83:299–365.
80. Bae T, et al. Identification of SAL200, a novel phage endolysin for anti-S. aureus therapy. Sci Rep. 2019;9(1):1–12.
81. Fowler VG, et al. Exebacase for patients with S. aureus bloodstream infection and endocarditis. J Clin Invest. 2020;130(7):3750–3760.
82. Chan BK, et al. Phage selection restores antibiotic sensitivity in MDR P. aeruginosa. Sci Rep. 2016;6:26717.
83. Lusiak-Szelachowska M, et al. Bacteriophage in the gastrointestinal tract. Gut Pathog. 2017;9(1):44.
84. Zuo T, et al. Gut mucosal virome alterations in ulcerative colitis. Gut. 2019;68(7):1169–1179.
85. Intralytix Inc. PhagoBiotic formulations for targeted microbiome modulation. Company Technical Report. 2023.