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The Silent Predators: A Comprehensive Review of Phage Therapy as a Public Health Tool Against MDR Bacteria

Victor Echezona Ike [1] and Ogonna Friday Okereke [2]

1. Department of Microbiology, Faculty of Science and Computing, University of Agriculture and Environmental Sciences, Umuagwo, Imo State

2. Department of Biological Sciences, Faculty of Natural and Applied Sciences, Spiritan University, Nneochi, Abia State

Email: victor.ike@uaes.edu.ng

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Abstract

The global rise of multidrug resistant (MDR) bacteria has outpaced the development of new antibiotics, creating an urgent need for alternative therapeutic strategies. Bacteriophage (phage) therapy, the use of viruses that specifically kill bacteria, represents a re-emerging approach with century-old roots but recent advances in manufacturing, regulatory pathways, and clinical evidence. This comprehensive review synthesizes evidence from 150 studies (2010–2025) examining the potential of phage therapy as a public health tool against MDR bacteria, including carbapenem-resistant Enterobacteriaceae (CRE), methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), extensively drug-resistant *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*. We analyze phage biology (host specificity, lytic vs. lysogenic cycles), clinical applications (compassionate use, personalized therapy, fixed cocktail preparations), safety data, and challenges (phage resistance, pharmacokinetics, regulatory hurdles). Evidence from compassionate use case series (n > 500 patients) shows clinical improvement in 70–90% of patients with otherwise untreatable MDR infections, with minimal adverse events. Recent randomized controlled trials for chronic wound infections and prosthetic joint infections confirm safety and suggest efficacy. We recommend establishing phage therapy as a regulated adjunct to antibiotics, investing in phage library infrastructure, developing standardized susceptibility testing, integrating phage therapy into AMR action plans, and funding high-quality RCTs. Phage therapy is not a replacement for antibiotics but a critically needed complement.

Keywords: Phage therapy; bacteriophages; multidrug resistant bacteria; antimicrobial resistance; personalized medicine; compassionate use

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Introduction

Antimicrobial resistance (AMR) has been declared one of the top ten global public health threats, with an estimated 1.27 million deaths directly attributable to bacterial AMR in 2019, a figure projected to reach 10 million annually by 2050 if no action is taken (Murray *et al.*, 2022; O'Neill, 2016). The pipeline for new antibiotics is alarmingly thin; only a handful of novel antibiotic classes have been approved in the past two decades, and most are derivatives of existing classes to which resistance has already emerged (Theuretzbacher *et al.*, 2023). Carbapenem-resistant Enterobacteriaceae (CRE), methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), extensively drug-resistant *Pseudomonas aeruginosa*, and multidrug-resistant *Acinetobacter baumannii* now circulate widely in hospitals and communities, leaving clinicians with few or no effective treatment options (WHO, 2024). In this context, bacteriophage (phage) therapy, the use of viruses that infect and kill bacteria, has re-emerged as a promising public health tool against MDR pathogens (Gordillo Altamirano & Barr, 2019; Kutter *et al.*, 2025).

Bacteriophages are the most abundant biological entities on Earth, discovered over a century ago by Félix d'Herelle, who used them to treat bacterial infections long before the advent of antibiotics (Sulakvelidze *et al.*, 2001). Phage therapy was largely abandoned in Western medicine following the widespread adoption of antibiotics in the 1940s, but it continued to be used and refined in Eastern Europe, particularly in Georgia (Eliava Institute), Poland, and Russia (Chanishvili, 2023). The current AMR crisis has sparked a renaissance in phage research, with major academic medical centers (University of California San Diego, Texas A&M, Yale, University of Pittsburgh), biotechnology companies, and regulatory agencies (FDA, EMA) actively developing and evaluating phage therapy (Strathdee *et al.*, 2023). Phages offer unique advantages over antibiotics: extreme specificity (they kill only target bacteria, sparing the microbiome), self-amplification at infection sites, minimal toxicity, and the ability to evolve alongside bacteria (can be engineered or selected to overcome bacterial resistance) (Dedrick *et al.*, 2025; Pirnay *et al.*, 2024).

This comprehensive review aims to synthesize the evidence on phage therapy as a public health tool against MDR bacteria. We address eight key questions: (1) What are the biological principles of phage therapy (lytic vs. lysogenic, host range, pharmacokinetics)? (2) What is the clinical evidence for phage therapy in MDR infections? (3) What are the safety and tolerability data? (4) How does bacterial resistance to phages emerge, and can it be mitigated? (5) What regulatory pathways exist for phage therapy (compassionate use, clinical trials, approved products)? (6) How does phage therapy compare to antibiotics in cost, accessibility, and scalability? (7) What are the barriers to widespread adoption (manufacturing, regulatory, reimbursement)? (8) What policies are needed to integrate phage therapy into national AMR action plans? We argue that phage therapy is not a replacement for antibiotics but a critically needed complement, and that establishing phage therapy as a regulated, accessible public health tool requires coordinated investment in infrastructure, clinical trials, and regulatory innovation.

General Review

2.1 Biological Principles of Phage Therapy

Bacteriophages are viruses that specifically infect bacteria. They are ubiquitous in nature (in water, soil, sewage, animal intestines) and have co-evolved with bacteria for billions of years (Salmond & Fineran, 2015). Phages used therapeutically must be lytic (kill bacteria by replicating inside them and causing lysis) rather than lysogenic (integrate their genome into the bacterial chromosome, potentially transferring virulence or resistance genes). Lytic phages are preferred for therapy because they cause rapid bacterial death and do not confer long-term genetic changes (Gordillo Altamirano & Barr, 2019). Host range varies from narrow (infect only a single strain of a single species) to broad (infect multiple species). For therapeutic applications, phages must be matched to the patient's bacterial isolate, either through pre-existing libraries or by screening environmental sources (Dedrick *et al.*, 2025).

Life cycle: phages adsorb to specific bacterial surface receptors (lipopolysaccharide, porins, pili, capsule), inject their genetic material, hijack bacterial machinery to produce phage components, assemble progeny phages, and lyse the bacterium, releasing 50–200 new phages per infection cycle

(Sulakvelidze *et al.*, 2001). Self-amplification is a key advantage: a single phage dose can amplify at the infection site as long as target bacteria remain. Pharmacokinetics: phages are cleared from the bloodstream rapidly (half-life 30–120 minutes) by the reticuloendothelial system (spleen, liver). Organ distribution favors the liver, spleen, kidneys, and lungs, with limited penetration into the central nervous system (unless inflammation disrupts the blood-brain barrier) (Dąbrowska, 2024). Intravenous administration is most effective for systemic infections; topical, inhaled, and intra-articular routes are used for localized infections (wounds, cystic fibrosis lung infections, prosthetic joints) (Pirnay *et al.*, 2024).

Immunogenicity: phages are immunogenic; antibodies against phages can develop within 1–3 weeks, potentially neutralizing subsequent doses. However, most patients receiving phage therapy for MDR infections have no pre-existing antibodies, and in the acute setting (sepsis, pneumonia), treatment duration is short (<7–14 days), limiting antibody impact (Strathdee *et al.*, 2023). For chronic infections (prosthetic joints, osteomyelitis), repeated courses may be limited by neutralizing antibodies (Dedrick *et al.*, 2025). Phage cocktails: combinations of multiple phages with complementary host ranges are used to broaden coverage, reduce the risk of resistance emergence, and treat infections caused by heterogeneous bacterial populations (Chan *et al.*, 2023). Fixed cocktails (pre-manufactured) are easier to regulate but may not cover all strains; personalized cocktails (manufactured on demand for a specific patient isolate) offer precision but are logistically complex (Pirnay *et al.*, 2024).

2.2 Clinical Evidence: Compassionate Use and Case Series

The majority of clinical evidence for phage therapy in MDR infections comes from compassionate use (emergency use for patients with no other treatment options) and case series, particularly from Eastern Europe (Georgia, Poland) and increasingly from the US and Europe. Georgia (Eliava Institute): the world's largest phage therapy center, treating over 10,000 patients since the 1930s. Published case series report clinical improvement (resolution of infection, microbiological cure) in 70–90% of patients with chronic infections (osteomyelitis, urinary tract infections, infected wounds, prosthetic joints) (Chanishvili, 2023). Poland (Hirszfeld

Institute) has treated over 1,000 patients, with efficacy of 75–85% for MDR *P. aeruginosa*, *S. aureus*, and *Klebsiella* infections (Międzybrodzki *et al.*, 2022).

US and European compassionate use (2015–2025): the largest series comes from the University of California San Diego (UCSD) Center for Innovative Phage Applications (CIPAA). A prospective case series of 100 patients with MDR infections (carbapenem-resistant *A. baumannii*, MRSA, VRE, MDR *P. aeruginosa*, MDR *E. coli*) treated with personalized phage cocktails reported clinical improvement in 87% (resolution of signs/symptoms, discharge from hospital, avoidance of amputation), microbiological clearance in 78%, and adverse events in 12% (mostly mild infusion reactions) (Strathdee *et al.*, 2023). A multi-center case series (US, Belgium, Australia, Israel, Canada) of 200 patients with MDR prosthetic joint infections, osteomyelitis, and infected implants reported clinical success in 72% (improvement without recurrence at 6 months) (Pirnay *et al.*, 2024).

Case studies of breakthrough responses: a young cystic fibrosis patient with disseminated MDR *M. abscessus* infection (pan-resistant, failing all antibiotics) received IV phage therapy (three engineered phages) with clearance of infection and return to normal life (Dedrick *et al.*, 2025). A patient with necrotizing pancreatitis complicated by carbapenem-resistant *A. baumannii* bacteremia (failing colistin and tigecycline) cleared infection within 48 hours of phage therapy (Schooley *et al.*, 2017). A liver transplant recipient with VRE bacteremia (failing linezolid, daptomycin, tigecycline) cleared infection after phage therapy (Aslam *et al.*, 2025). These dramatic responses in terminally ill patients have driven regulatory and clinical interest.

Limitations of compassionate use evidence: lack of control groups, selection bias (patients who improve are more likely to be reported), publication bias (positive outcomes more likely published), and variability in outcome definitions. However, for patients with no treatment options, placebo-controlled trials are ethically challenging. The evidence base is strengthening but remains lower quality than for approved antibiotics (Pirnay *et al.*, 2024).

2.3 Randomized Controlled Trials: Emerging Evidence

Several randomized controlled trials (RCTs) of phage therapy have been completed or are ongoing. Diabetic foot ulcer infections: a Phase I/II RCT (US, 50 patients) of a fixed phage cocktail (active against *S. aureus*, *P. aeruginosa*, *E. coli*) applied topically to chronic diabetic foot ulcers found no difference in ulcer healing between phage and placebo at 12 weeks (45% vs. 42%, p=0.78) but a trend toward reduced infection-related amputations (6% vs. 15%, p=0.09) (Fish *et al.*, 2025). The authors noted that the placebo group received standard wound care (including antibiotics), which may have confounded results.

Prosthetic joint infections (PJI): a Phase II RCT (Belgium, 60 patients) of adjunctive phage therapy (single intraoperative injection) added to standard two-stage exchange arthroplasty for chronic PJI. The phage group had 32% infection-free survival at 12 months compared to 28% in the control group (p=0.42), not statistically significant. However, a post hoc analysis of patients with identifiable bacteria in the phage cocktail's host range showed 52% infection-free survival (p=0.04) (Onsea *et al.*, 2024). This underscores the importance of matching phages to the infecting strain.

Chronic otitis media: a double-blind RCT (UK, 100 patients) of a fixed phage cocktail (active against *P. aeruginosa*) applied as ear drops for chronic suppurative otitis media found that phage treatment achieved clinical cure in 67% of patients vs. 45% with placebo (p=0.03) and reduced *P. aeruginosa* colony counts by 4 logs (vs. 1 log in placebo) (Wright *et al.*, 2024). This is the most positive phage RCT to date. Cystic fibrosis lung infections: an ongoing Phase II RCT of inhaled phage therapy for chronic *P. aeruginosa* colonization (US, 120 patients) is expected to report in 2026.

Challenges in phage RCTs: (1) Patient heterogeneity (infections caused by different bacteria, different phage susceptibility); (2) Need for rapid phage susceptibility testing to enroll patients with phage-sensitive isolates; (3) Difficulty blinding (phage solutions have characteristic appearance, but sham phages can be used); (4) Ethical concerns with placebo arms in severe infections; (5) Adaptive trial designs are needed but not yet standard (Pirnay *et al.*, 2024). Despite challenges, RCT evidence is accumulating and will be essential for regulatory approval.

2.4 Safety and Tolerability

Phage therapy has an excellent safety profile across thousands of patients treated over decades. Adverse events in compassionate use series: mild infusion reactions (fever, chills, hypotension) in 5–15%, generally transient and responsive to antipyretics; no anaphylaxis or cytokine storm reported; no phage-attributed deaths (Strathdee *et al.*, 2023). Toxicity studies in animal models show no organ toxicity, mutagenicity, or teratogenicity; phages are generally recognized as safe (GRAS) by the FDA for food applications (Sulakvelidze *et al.*, 2001). Potential safety concerns: (1) Endotoxin release from bacterial lysis (Jarisch-Herxheimer reaction) can cause transient fever and hypotension. Mitigation: use highly purified phages (less than 10 endotoxin units/mL); co-administer anti-inflammatory agents (steroids) for severe infections. (2) Lysogenic conversion (integration of phage DNA into bacterial chromosome) could transfer virulence or antibiotic resistance genes. Mitigation: use only lytic phages (contain no integrase genes). All therapeutic phages are genomically sequenced to exclude lysogeny genes (Dedrick *et al.*, 2025). (3) Immune neutralization (anti-phage antibodies) can reduce efficacy of repeat dosing. Mitigation: short treatment duration; use of phage cocktails (multiple phages reduce impact of antibodies to any single phage). (4) Bacterial resistance to phages emerges rapidly (discussed below) (Chan *et al.*, 2023).

Special populations: immunocompromised patients (neutropenia, transplant recipients, HIV) have tolerated phage therapy without unusual adverse events. No interactions with antibiotics or immunosuppressive agents have been reported (Aslam *et al.*, 2025). Pregnancy and pediatrics: limited data. Several pregnant patients with pyelonephritis received phage therapy without maternal or fetal adverse events; case series of pediatric patients (cystic fibrosis, osteomyelitis) show safety comparable to adults (Międzybrodzki *et al.*, 2022). The safety profile of phages is far superior to that of last-line antibiotics (colistin nephrotoxicity, aminoglycoside ototoxicity, tigecycline gastrointestinal toxicity), making phage therapy particularly attractive for vulnerable patients.

2.5 Bacterial Resistance to Phages and Mitigation Strategies

Bacteria can evolve resistance to phages through mutations in surface receptors (phage binding sites), restrictionmodification systems (cutting foreign DNA), CRISPR-Cas systems (adaptive immunity), or abortive infection pathways (programmed cell death). Resistance emergence is common in vitro (within hours to days) and has been observed in clinical cases (Dedrick *et al.*, 2025; Chan *et al.*, 2023). However, resistance to phages is not a dead end for therapy: (1) Fitness trade-offs: mutations conferring phage resistance often reduce bacterial virulence (altered capsule, reduced adherence, increased antibiotic susceptibility) or restore antibiotic susceptibility (reversal of carbapenem resistance in *A. baumannii*). A study of phage-resistant *P. aeruginosa* showed 10- to 100-fold reduced virulence in a mouse pneumonia model (Gordillo Altamirano & Barr, 2019). (2) Phage cocktails: using multiple phages targeting different receptors reduces the probability of resistance (the bacterium must mutate multiple receptors simultaneously). In vitro experiments show that phage cocktails suppress resistance for 20–100 times longer than single phages (Chan *et al.*, 2023). (3) Phage training and evolution: phages can be evolved in the laboratory to recognize new receptors ("phage training") or can co-evolve with bacteria during therapy (bacteria mutate, phages counter-mutate). In a compassionate use case, a patient with MDR *M. abscessus* received three engineered phages; when resistance emerged to one phage, the phage was re-evolved and re-administered, clearing the infection (Dedrick *et al.*, 2025). (4) Phage-antibiotic synergy: subinhibitory concentrations of antibiotics can suppress phage resistance (antibiotics kill resistant mutants) or make bacteria more susceptible to phages (antibiotics disrupt cell wall, enhancing phage adsorption). Combinations of phages and antibiotics show additive or synergistic effects in animal models (Aslam *et al.*, 2025). (5) Rapid susceptibility testing: next-generation sequencing and quantitative PCR can identify resistance mutations early, allowing clinicians to switch phages (cocktail adjustment) before clinical failure.

Clinical resistance experience: in the UCSD case series, bacterial resistance to one or more phages in the cocktail was detected in 25% of patients, but most remained susceptible to at least one phage in the cocktail, and clinical failure due solely to resistance was rare (5%) (Strathdee *et al.*, 2023). Resistance is manageable with current strategies; it is not a contraindication to phage therapy.

2.6 Regulatory Pathways for Phage Therapy

Regulatory frameworks for phage therapy vary globally and are evolving rapidly. United States (FDA): phages are regulated as biological products (not drugs). The FDA has approved phage therapy under three pathways: (1) Emergency Investigational New Drug (eIND): for individual patients with immediately life-threatening MDR infections and no alternative therapy. 200+ eIND applications have been approved since 2015 (Strathdee *et al.*, 2023). (2) Phase I/II/III clinical trials: several are ongoing (diabetic foot ulcers, prosthetic joint infections, cystic fibrosis). (3) Staggered approval pathway: the FDA designated a fixed phage cocktail for *S. aureus* as a "breakthrough therapy" in 2024. (4) Compassionate use expanded access program: allows treatment of multiple patients under a single protocol. The FDA has been highly supportive of phage therapy development (Pirnay *et al.*, 2024).

European Union (EMA): phages are regulated as medicinal products. The EMA has approved phage therapy under: (1) Hospital exemption (Article 5 of Regulation 726/2004 allows individual compassionate use); (2) Clinical trials; (3) Marketing authorization (none yet approved). The Belgian and French governments have national phage therapy frameworks (phage libraries, centralized manufacturing, reimbursement) (Pirnay *et al.*, 2024). Georgia and Poland have long-standing national phage therapy centers operating under local regulations (not EMA). Australia (TGA): phages are regulated as biologicals; several eIND approvals. Guidance documents: WHO published "Regulatory considerations for bacteriophage therapy" in 2024, calling for harmonized frameworks (WHO, 2024).

Manufacturing challenges: phages must be produced in living bacterial hosts, requiring Good Manufacturing Practice (GMP) facilities with biosafety level 2 (BSL-2). Purification to remove endotoxin and bacterial debris is essential. Standardized phage susceptibility testing (similar to antibiotic MIC testing) is lacking but under development (Chan *et al.*, 2023). Reimbursement: phage therapy is not yet covered by insurance in most countries; costs are borne by research grants, hospitals, or philanthropies. Cost-effectiveness analyses show phage therapy is cheaper than prolonged ICU care for MDR sepsis (10,000–30,000*percoursevs.*100,000–500,000 for prolonged hospitalization) (Międzybrodzki *et al.*, 2022). Integration into national health systems requires reimbursement pathways.

2.7 Phage Therapy as a Public Health Tool: Infrastructure Needs

To deploy phage therapy at scale as a public health tool against MDR bacteria, significant infrastructure investments are needed. Phage libraries: national or regional libraries of well-characterized lytic phages against WHO priority pathogens (*A. baumannii*, *P. aeruginosa*, Enterobacteriaceae, MRSA, VRE, *M. abscessus*). Libraries should include genomic sequences (no toxin or lysogeny genes), host range data (tested against >1,000 clinical isolates), and manufacturing protocols (Chan *et al.*, 2023). The US Navy's phage library (1,000+ phages) and the Belgian phage library (500+ phages) are models. Rapid phage susceptibility testing: clinical microbiology labs need standardized assays to determine if a patient's isolate is susceptible to available phages (similar to antibiotic disk diffusion or MIC). Phage plaque assays take 12–24 hours; rapid PCR-based detection of phage receptor genes is under development (Dedrick *et al.*, 2025).

Centralized manufacturing and distribution: GMP phage production is complex; regional centers (1–2 per country) with capacity to produce clinical grade phages within 48–72 hours of receiving a patient's bacterial isolate are needed. The UCSD "phage phactory" and the Belgian "Phage Therapy Unit" are prototypes (Strathdee *et al.*, 2023). Clinical training: infectious disease physicians, pharmacists, and microbiologists need training in phage therapy indications, administration, and monitoring. Formal curricula are being developed (Pirnay *et al.*, 2024).

Cost considerations: a personalized phage course costs 10,000–50,000(*strainisolation*, *libraryscreening*, *GM*
5,000–20,000 per course). For comparison, a course of ceftazidime-avibactam for carbapenem-resistant *Klebsiella* costs 5,000–15,000; *prolongedICUcareforMDRsepsiscosts*
100,000–500,000. Phage therapy is cost-effective for last-line indications (Międzybrodzki *et al.*, 2022). Global access: high costs and infrastructure requirements limit access in LMICs, where MDR burden is highest.

Decentralized low-cost production (using non-GMP facilities for compassionate use) has been proposed but raises regulatory concerns (Chan *et al.*, 2023). WHO should establish a global phage therapy access fund.

2.8 Phage Therapy in LMICs and Resource-Limited Settings

Paradoxically, phage therapy has been used for decades in LMICs (Georgia, Poland, Russia) but remains inaccessible in most low-income countries where MDR rates are highest (sub-Saharan Africa, South Asia). The barriers are not scientific but economic and regulatory. Georgia model: low-cost, high-volume phage production (non-GMP but safe for over 80 years) treats tens of thousands of patients annually for chronic MDR infections (Chanishvili, 2023). The Georgian phage cocktails (Sextaphage, Pyophage, Intestiphage) are marketed over the counter for topical and oral use. Safety record is excellent, but lack of GMP production limits export. Potential for LMICs: decentralized production using low-resource methods (sterile media, simple bioreactors) is feasible. The non-profit organization "Phages for Global Health" is training African labs in phage isolation and production (Phages for Global Health, 2025).

Case study: India, where carbapenem-resistant *Klebsiella* and *A. baumannii* are endemic, with mortality rates >50% for bloodstream infections. A pilot phage therapy program at a Mumbai hospital treated 20 patients with MDR sepsis; 14 (70%) survived, compared to historical survival of 20–30% (Aslam *et al.*, 2025). Barriers to scale in LMICs: lack of regulatory pathways, lack of diagnostic capacity for phage susceptibility testing, lack of trained personnel, and cost of GMP production. Solutions: regional phage banks (shared among neighboring countries); technology transfer from high-income countries; WHO prequalification for phage products; and tiered regulatory pathways (non-GMP for compassionate use, GMP for registration) (WHO, 2024).

Community-acquired MDR infections: in LMICs, MDR bacteria are not just hospital-acquired; community-acquired infections (urinary tract infections, pneumonia, diarrhea) are increasingly drug-resistant. Fixed phage cocktails could be used as over-the-counter treatments for uncomplicated infections (e.g., *E. coli* cystitis), reducing antibiotic use and selection pressure for resistance. This "phage first" approach is being piloted in Bangladesh for cholera (phage prophylaxis for household contacts) (Kutter *et al.*, 2025).

2.9 Comparison with Antibiotics and Other Alternatives

Phage therapy is not a replacement for antibiotics but a complement, with distinct advantages and disadvantages.

Feature	Phage Therapy
Spectrum	Narrow (specie
Effect on microbiome	Minimal
Self-amplification	Yes (at infectio
Resistance emergence	Rapid but costs)
Activity against biofilms	High (penetra bacteria)
Safety	Excellent (minimal toxicity)
Manufacturing	Complex (needs bacterial GMP)
Regulatory status	Not yet approved (compassi use)
Cost per course	High ($10,000–50,000 personalized)
Physician familiarity	Low

Phages vs. other alternatives: antimicrobial peptides (AMPs) have narrow therapeutic windows (toxicity); monoclonal antibodies are expensive and restricted to a single target; microbiome transplants (FMT) are effective only for *C. difficile*; predatory bacteria are investigational. Phages offer the best balance of specificity, safety, and adaptability (Gordillo Altamirano & Barr, 2019).

Combination therapy: phages and antibiotics are synergistic. In a mouse pneumonia model, phage-antibiotic combinations (phage + meropenem for carbapenem-resistant *K. pneumoniae*) reduced bacterial load by 8 logs vs. 3–4 logs for either alone (Chan *et al.*, 2023). In patients, phage therapy is almost always added to existing antibiotic regimens; withdrawal of antibiotics after phage response is rare. Combination therapy delays resistance to both agents (phage resistance restores antibiotic sensitivity; antibiotic resistance may increase phage sensitivity) (Aslam *et al.*, 2025).

2.10 Gaps, Challenges, and Future Directions

Despite progress, critical gaps remain. High-quality RCTs are urgently needed for definitive evidence of efficacy. Adaptive platform trials (testing multiple phages across multiple indications) are more efficient than traditional RCTs. Standardized susceptibility testing (CLSI/EUCAST equivalents for phages) is essential for clinical microbiology labs. Regulatory harmonization: international guidelines for phage manufacturing, quality control, and clinical indications are needed. WHO's 2024 guidance is a first step.

Phage engineering: synthetic biology can enhance phages (receptor-binding protein modification to expand host range, deletion of toxin genes, addition of biofilm-degrading enzymes). CRISPR-Cas armed phages can selectively kill antibiotic-resistant bacteria (Dedrick *et al.*, 2025). Phage prodrugs: phages encoding antibiotic sensitivity genes (restoring susceptibility to beta-lactams in carbapenem-resistant bacteria) are in preclinical development (Chan *et al.*, 2023). Phage delivery: long-acting formulations (liposomal encapsulation, hydrogels) for sustained release; nebulized phages for lung infections; oral formulations (acid-resistant capsules) for gastrointestinal infections are under development.

Public and clinician education: many clinicians are unfamiliar with phage therapy; misconceptions (phages are dangerous, unregulated, ineffective) persist. Professional society guidelines (IDSA, ESCMID, SHEA) are needed. Surveillance: national AMR surveillance systems should include phage susceptibility testing for sentinel isolates to map resistance patterns and guide cocktail design. Phage biobanks: long-term sustainability requires funding for maintenance of phage libraries (freeze-drying, cryopreservation). Global access: WHO should establish a "Phage Therapy Access Facility" similar to the Global Fund for HIV/TB/Malaria, supporting LMIC infrastructure, training, and product supply.

Conclusion

Phage therapy has re-emerged as a promising tool against multidrug-resistant bacteria, offering safety, specificity, self-amplification, and biofilm activity. Evidence from compassionate use shows 70–90% clinical improvement in otherwise untreatable infections, with early RCTs supporting efficacy for chronic otitis media and prosthetic joint infections when phages are matched to the pathogen. Resistance is manageable through cocktails, synergy with antibiotics, and phage engineering. Phage therapy is not a replacement for antibiotics but a critically needed complement. Widespread adoption requires infrastructure investment (phage libraries, GMP manufacturing, susceptibility testing), regulatory harmonization, and equitable global access. With coordinated commitment, phage therapy can become a standard tool against the AMR crisis.

Recommendations

Based on the evidence synthesized in this review, the following recommendations are offered for governments, regulators (FDA, EMA, WHO), healthcare systems, researchers, and funders:

1. Establish national phage therapy programs including centralized phage libraries (500–1,000 lytic phages against WHO priority pathogens), GMP manufacturing capacity, and rapid susceptibility testing services. Model after Belgian and UCSD programs.

2. Integrate phage therapy into national AMR action plans as a complementary strategy to antibiotic stewardship and infection prevention. Allocate dedicated funding for infrastructure, clinical trials, and compassionate use.

3. Accelerate regulatory approval pathways: FDA/EMA should create a "phage therapy" designation with streamlined requirements for manufacturing

changes (when phages in a cocktail are substituted), given that bacteria evolve and phages must adapt.

4. Fund high-quality randomized controlled trials for priority indications: prosthetic joint infections, cystic fibrosis lung infections, diabetic foot ulcers, and carbapenem-resistant Enterobacteriaceae bloodstream infections. Use adaptive platform designs.

5. Develop standardized phage susceptibility testing (CLSI/EUCAST guidelines) for clinical microbiology labs. Include phage susceptibility in AMR surveillance systems.

6. Support phage-antibiotic combination research to identify synergistic pairs, optimal dosing, and resistance suppression strategies. Translate preclinical findings into clinical protocols.

7. Invest in phage engineering (CRISPR-Cas phages, receptor-binding protein modification, biofilm-degrading enzymes) to enhance efficacy and overcome resistance. Prioritize phages against pan-resistant *A. baumannii*, *P. aeruginosa*, and *K. pneumoniae*.

8. Create a global phage therapy access fund (modeled on the Global Fund, PEPFAR) to support LMIC infrastructure, training, and product supply. Ensure equitable access to phage therapy.

9. Train infectious disease physicians and pharmacists in phage therapy indications, administration, and monitoring. Include phage therapy in medical school and residency curricula.

10. Publish clinical outcomes (including negative results) in registries to build the evidence base. The Phage Therapy Outcomes Registry (PTOR) should be expanded globally.

11. Establish WHO prequalification and international standards for phage manufacturing, quality control, and clinical indications. Harmonize regulatory frameworks across countries.

12. Reimburse phage therapy through national health insurance and private payers. Include phage therapy in hospital formularies for MDR infections with no alternative therapy.

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