PHAGE THERAPY IN COMBATING ANTIMICROBIAL RESISTANCE: A ONE HEALTH APPROACH

Pragya Mishra*, Satvik Narayan Tiwari, Vallabhaneni Srikanth
ICAR-Indian Veterinary Research Institute, Bareilly, Uttar Pradesh
*Corresponding author's email: *pragyamishra5643@gmail.com*
DOI: https://doi.org/10.5281/zenodo.20686692

Abstract

Antimicrobial resistance (AMR) has become a major global health concern of the 21st century, threatening the effective treatment of infectious diseases in both humans and animals. The extensive and often indiscriminate use of antibiotics in human medicine, veterinary practice and agriculture has accelerated the emergence of multidrug-resistant (MDR) pathogens, leading to increased morbidity, mortality and economic losses worldwide. The declining efficacy of conventional antibiotics has created an urgent need for alternative antimicrobial strategies that are effective, safe, and sustainable. Among the promising alternatives, bacteriophage therapy has re-emerged as a potential biological approach to combat antibiotic-resistant infections. Bacteriophages or Phages are viruses that specifically infect and lyse bacterial cells, offering advantages such as high host specificity, self-replication at the site of infection and the ability to disrupt bacterial biofilms. Phage therapy has demonstrated potential in managing bacterial infections in human and veterinary medicine including mastitis, respiratory infections, gastrointestinal diseases and wound infections. Additionally, phage therapy has demonstrated potential in controlling bacterial contamination in food processing environments and enhancing biosecurity in animal farming systems. Despite its potential, challenges such as regulatory limitations, limited host range and standardization issues remain. Continued research and policy support are essential to facilitate the safe and effective integration of phage therapy into antimicrobial resistance management strategies.

Keywords: Alternative therapeutics, antimicrobial resistance, bacteriophages, multidrug resistance, one Health, Veterinary medicine

Introduction

Antimicrobials, including antibiotics, antivirals, antifungals and antiparasitics, are medicines used to prevent and treat infectious diseases in humans, animals and plants. Antimicrobial resistance (AMR) occurs when microorganisms no longer respond to these medicines, making infections difficult to treat. AMR is a major global public health threat, responsible for about 1.27 million deaths and associated with 4.95 million deaths worldwide in 2019, with projections of up to 10 million deaths annually by 2050, alongside substantial economic losses, including additional healthcare costs of up to US$ 1 trillion by 2050 and annual global GDP losses of US$ 1 trillion to US$ 3.4 trillion by 2030 (WHO). The rapid rise of AMR is largely driven by human behaviour, particularly the misuse and overuse of antibiotics, which has promoted the emergence of MDR bacteria. Among the most significant contributors are the ESKAPE pathogens viz., *Enterococcus faecium, Staphylococcus aureus* (including MRSA), *Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa* and *Enterobacter* spp., known for evading antibiotic action, forming resilient biofilms and causing severe hospital-acquired infections with high morbidity and mortality.

In response to the growing AMR crisis and the declining development of new antibiotics, alternative antibacterial strategies are urgently needed. The antibiotic pipeline has slowed considerably, with only eight drugs approved by the FDA between 2010 and 2015 compared to numerous approvals during the

1980s (Deak et al., 2016). One promising alternative is phage therapy, which employs bacteriophages, viruses that specifically infect and destroy bacteria. Phages were independently discovered by Frederick Twort in 1915 and Félix d'Herelle in 1917, who coined the term "bacteriophage" and first used it to treat bacterial dysentery in 1919. Phage therapy was widely applied during the 1920s and 1930s but declined after the introduction of penicillin in the 1940s due to the convenience of antibiotics and inconsistent early results. Today, the escalating threat of AMR has renewed global interest in this century-old therapeutic approach (Patel et al., 2025).

What Are Bacteriophages ?

Bacteriophages (or phages) are viruses that specifically infect, replicate within and kill bacteria. Discovered over a century ago, they are the oldest and most abundant biological entities on the planet, with an estimated 10^{31} virions distributed throughout the biosphere. Because they are strict parasites of bacteria, phages do not infect human cells (Principi et al., 2019). Bacteriophages have a distinctive tadpole-like structure (Fig.1) with a polyhedral head (capsid) that protects their genome, a tail for attachment and DNA injection, and tail fibers for bacterial recognition. The head is an icosahedral protein shell (20 faces), typically 50-100 nm across, containing the genome; the tail (sometimes contractile sheath + inner tube) connects via a collar to a baseplate with spikes and fibers that bind specific bacterial receptors. Phage genomes are relatively small and tightly packed, most commonly consisting of double-stranded DNA (dsDNA), though RNA genomes also exist.

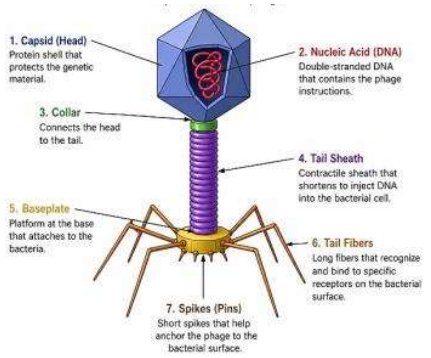

Fig. 1 Structure of a bacteriophage

What's the Mechanism of Action of Phage Therapy ?

Phage therapy controls bacterial infections through multiple mechanisms, particularly against multidrug-resistant (MDR) pathogens. Bacteriophages attach to specific receptors on bacterial cells, inject their genetic material (Fig.2) and use the host machinery to replicate. Enzymes such as endolysins then break the bacterial cell wall, causing cell lysis and release of new phages that infect nearby bacteria. Phages can also disrupt biofilms by producing depolymerase enzymes that degrade the protective matrix surrounding bacterial communities. Their high specificity allows targeted elimination of pathogens while preserving beneficial microbiota. Phages multiply at the infection site as long as susceptible bacteria are present and can enhance antibiotic effectiveness through *phage-antibiotic synergy*. These properties, including targeted killing, self-replication and low toxicity, make phage therapy a promising strategy for managing antimicrobial-resistant infections, particularly in severe hospital-acquired infections where antibiotics are ineffective.

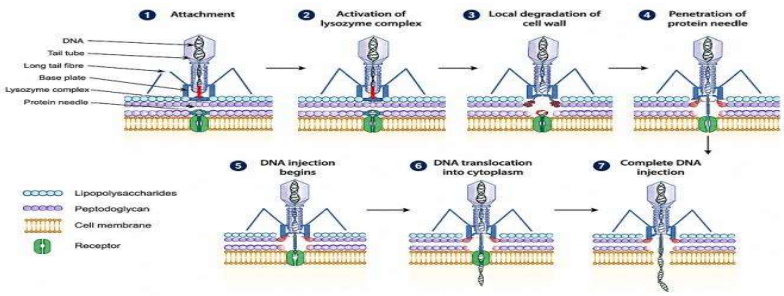

Fig. 2 Mechanism of Bacteriophage Infection: DNA Injection into the Bacterial Host Cell

How the Phages can be delivered into the living system ?

Phage therapy can be administered through multiple routes depending on the infection site including oral, topical, intranasal or inhalation, intravenous, intravesical, ocular (eye drops), otic (ear drops), intramuscular, rectal and vaginal routes. Selection of the route is guided by the site of infection, disease severity, and therapeutic objectives. Phages can be prepared in wide variety of delivery systems which are tabulated below:

Phage Delivery System	Forms
Liquid suspensions	Saline/ Phosphate-buffered saline (PBS), SM buffer
Lyophilized formulations	Freeze-dried phage preparations
Liposome-based systems	Conventional / Cationic liposomes, Liposome-phage nanoconjugates
Hydrogel-based systems	Carbopol hydrogel, Polymer hydrogels, Ocular gels
Polymer-based encapsulation	Biopolymer and synthetic polymer carriers
Nanofiber-based systems	Electro spun nanofiber mats
Phage-coated biomaterials	Wound dressings, Catheters, Medical implants
Aerosol and inhalation systems	Nebulized phage formulations, Pulmonary sprays
Nano emulsion-based systems	Oil-in-water nano emulsions
Lipid-based nanocarriers	Solid lipid nanoparticles (SLNs), Nanostructured lipid carriers (NLCs)

What are the Advantages and Limitations of Phage Therapy ?

While phage therapy shows significant potential in combating antimicrobial resistance, it is associated with both benefits and challenges that influence its practical application. The key advantages and limitations of phage therapy are outlined in the table below.

Advantages of Phage Therapy

- ✓ High specificity to target bacteria, minimizing damage to beneficial microbiota
- ✓ Effective against MDR bacteria
- ✓ Ability to replicate at the site of infection (self-amplifying)
- ✓ Capable of disrupting bacterial biofilms
- ✓ Reduced side effects compared to antibiotics
- ✓ Minimal impact on normal microbiota
- ✓ Can be used in combination with antibiotics (phage-antibiotic synergy)
- ✓ Environmentally friendly and naturally occurring agents
- ✓ Potential for personalized therapy
- ✓ Low toxicity to humans and animals

Limitations / Challenges of Phage Therapy

- × Narrow host range requiring precise pathogen identification
- × Bacteria may develop resistance to phages over time
- × Potential immune response against phages
- × Regulatory and approval challenges in many countries
- × Lack of standardized dosing and treatment protocols
- × Stability and storage issues under certain environmental conditions
- × Limited large-scale clinical trial data
- × Manufacturing and quality control complexities
- × Need for phage libraries or banks for rapid selection
- × Risk of horizontal gene transfer in some phages

What are the Applications of Phage Therapy ?

Phage therapy has diverse applications in human medicine, veterinary practice and food safety and agriculture due to its ability to specifically target bacterial pathogens, including multidrug-resistant strains. In human medicine, bacteriophages are used in the management of skin infections, respiratory infections, urinary tract infections, wound infections, and sepsis, particularly in cases where antibiotics are ineffective. In veterinary medicine, phage therapy is applied to control diseases such as mastitis, diarrhea, respiratory infections, poultry infections, and aquaculture diseases, helping to improve animal health and reduce antibiotic usage in livestock production systems, which is especially relevant to veterinary and animal science fields. In food safety and agriculture, phages are used for the control of foodborne pathogens, reduction of meat contamination, improvement of dairy safety, and protection of crops, thereby enhancing food quality and supporting sustainable agricultural practices.

What about Current Research and Evidence ?

1. ***Laboratory Studies:*** In vitro studies demonstrate that bacteriophages effectively kill target bacteria, often outperforming antibiotics against multidrug-resistant strains and biofilms. Lytic phages can reduce bacterial loads by 3–5 log units within 24–48 hours, and phage cocktails help prevent resistance development and enhance biofilm disruption in *S. aureus* and *P. aeruginosa* models (Gliźniewicz *et al., 2024*).
2. ***Animal Studies:*** Preclinical studies in animal models such as mice and rats confirm the effectiveness of phage therapy across different infection sites. Phage treatment achieved 80–100% survival in *Pseudomonas aeruginosa* pneumonia models (Melo *et al., 2020*), improved clearance of MRSA wound infections, and prevented *Escherichia coli* sepsis when administered prophylactically (Wang *et al., 2006*), although immune clearance may limit systemic effects (Melo *et al., 2020*).
3. ***Human Clinical Studies:*** Case reports and small clinical trials report significant clinical improvement and bacterial eradication, particularly in compassionate use for multidrug-resistant infections. Successful outcomes include prosthetic joint salvage and healing of diabetic foot ulcers, with treatments generally well tolerated and no treatment-related adverse events (Aslam *et al., 2018*).
4. ***Gaps in Evidence:*** Despite encouraging findings, current evidence remains limited due to the lack of large randomized controlled trials, variability in dosing ranges (10^8–10^{11} PFU), and insufficient long-term follow-up data. Challenges such as polymicrobial infections, delivery optimization, and cost-effectiveness continue to hinder regulatory approval and routine clinical implementation.

What are the Future Scope and Perspectives of Phage Therapy?

The future of phage therapy depends on advances in rapid phage selection, combination treatments, genetic engineering and clinical standardization. Automated phagotyping and artificial intelligence-based matching, supported by global phage banks, can enable faster development of personalized therapies (Getz et al., 2025). Combining phages with antibiotics, nanoparticles, or antimicrobial peptides has shown improved effectiveness against pathogens such as *Pseudomonas aeruginosa* and *Staphylococcus aureus* (Bhargava et al., 2021). Genetic engineering approaches, including CRISPR-modified phages and phage-derived lysins, offer enhanced antibacterial activity against resistant infections, including MRSA (Anastassopoulou et al., 2025; Marais, 2021). Wider clinical adoption will require standardized manufacturing, regulatory support, and well-designed clinical trials to integrate phage therapy into routine treatment

of multidrug-resistant infections (Bretaudeau et al., 2020).

Adoption within the One Health approach will enable coordinated control of resistant pathogens across human, animal, and environmental sectors. The establishment of well-organized phage banks with genomic characterization will support rapid identification of suitable phages for treatment and outbreak response. Advances in precision medicine are expected to facilitate personalized phage therapy tailored to specific pathogens and patient conditions. Future research should focus on optimizing delivery systems, standardizing dosing protocols, improving large-scale production, and generating robust clinical evidence to support safe and effective use.

Conclusion

Phage therapy is no longer just a scientific curiosity; it is increasingly viewed as a serious response to one of modern medicine's most urgent crises i.e. Antimicrobial resistance. Unlike broad-spectrum antibiotics, phages are highly specific, attacking only their bacterial targets while leaving most of the surrounding microbiome untouched. That precision makes them especially valuable in an era when drug-resistant infections are rising worldwide and treatment options are shrinking. Yet despite its promise, phage therapy is not a simple cure-all. Questions around safety, standardization, regulation, and the evolution of bacterial resistance to phages still need careful attention before the field can fully mature . Even so, the renewed scientific momentum behind phage research reflects a larger truth: some of the most powerful solutions to today's medical challenges may come from revisiting ideas nature has refined for billions of years. As research advances, phage therapy may well become an essential part of the future toolkit against resistant infections.

References

Abedon, S. T., Danis-Wlodarczyk, K. M., & Alves, D. R. (2021). Phage therapy in the 21st century: is there modern, clinical evidence of phage-mediated efficacy?. *Pharmaceuticals*, *14*(11), 1157.

Anastassopoulou, C., Tsakri, D., Panagiotopoulos, A. P., Saldari, C., Sagona, A. P., & Tsakris, A. (2025). Armed phages: A new weapon in the battle against antimicrobial resistance. *Viruses*, *17*(7), 911.

Aslam, S., Gilbey, T., Maddocks, S., Morales, S., Lehman, S., Branston, S., ... & Iredell, J. (2018, November). 1642. Safety and efficacy of bacteriophage therapy: analysis of clinical case series data. In *Open Forum Infectious Diseases* (Vol. 5, No. Suppl 1, p. S47).

Bhargava, K., Nath, G., Bhargava, A., Aseri, G. K., & Jain, N. (2021). Phage therapeutics: from promises to practices and prospectives. *Applied Microbiology and Biotechnology*, *105*(24), 9047-9067.

Bretaudeau, L., Tremblais, K., Aubrit, F., Meichenin, M., & Arnaud, I. (2020). Good manufacturing practice (GMP) compliance for phage therapy medicinal products. *Frontiers in microbiology*, *11*, 1161.

Deak, D., Outterson, K., Powers, J. H., & Kesselheim, A. S. (2016). Progress in the fight against multidrug-resistant bacteria? A review of US Food and Drug Administration–approved antibiotics, 2010–2015. *Annals of internal medicine*, *165*(5), 363-372.

Donati, V. L. (2021). Bacteriophage-based control of Flavobacterium psychrophilum in rainbow trout: Studies on phage-treatment of rainbow trout at fry and eyed egg stages and effects on gut microbial communities.

Getz, L. J., Patel, P. H., & Maxwell, K. L. (2025). A solution to the postantibiotic era: phages as precision medicine. *Current Opinion in Microbiology*, *86*, 102613.

Hashiguchi, T. C. O., Ait Ouakrim, D., Padget, M., Cassini, A., & Cecchini, M. (2019). Resistance proportions for eight priority antibiotic-bacterium combinations in OECD, EU/EEA and G20 countries 2000 to 2030: a modelling study. *Eurosurveillance*, *24*(20), 1800445.

Hibstu, Z., Belew, H., Akelew, Y., & Mengist, H. M. (2022). Phage therapy: a different approach to fight bacterial infections. *Biologics: Targets and Therapy*, 173-186.

Marais, L. C. (2021). Antibiotic resistance-Netflix, HAL 9000 and the $100 billion question. *SA Orthopaedic Journal*, *20*(3), 126-128.

Melo, L. D., Oliveira, H., Pires, D. P., Dabrowska, K., & Azeredo, J. (2020). Phage therapy efficacy: a review of the last 10 years of preclinical studies. *Critical reviews in microbiology*, *46*(1), 78-99.

Oechslin, F. (2018). Resistance development to bacteriophages occurring during bacteriophage therapy. *Viruses*, *10*(7), 351.

Patel, R. R., Arun, P. P., Singh, S. K., & Singh, M. (2025). Overcoming antimicrobial resistance: Phage therapy as a promising solution to combat ESKAPE pathogens. *International Journal of Antimicrobial Agents*, 107640.Pires, D. P., Melo, L. D., Boas, D. V., Sillankorva, S., & Azeredo, J. (2017). Phage therapy as an alternative or complementary strategy to prevent and control biofilm-related infections. *Current opinion in microbiology*, *39*, 48-56.

Principi, N., Silvestri, E., & Esposito, S. (2019). Advantages and limitations of bacteriophages for the treatment of bacterial infections. *Frontiers in pharmacology*, *10*, 457104.

Rezaei, A. R. (2024). Bacteriophages for the treatment of resistant bacterial infectious diseases. *Journal of Bacteriology and Virology*, *54*(2), 84-93.

Smith, R. A., M'ikanatha, N. M., & Read, A. F. (2015). Antibiotic resistance: a primer and call to action. *Health communication*, *30*(3), 309-314.

Wang, J., Hu, B. E. I., Xu, M., Yan, Q. U. N., Liu, S., Zhu, X., ... & Hu, J. (2006). Therapeutic effectiveness of bacteriophages in the rescue of mice with extended spectrum β-lactamase-producing Escherichia coli bacteremia. *International journal of molecular medicine*, *17*(2), 347-355.

Cite this article:
Pragya Mishra, Satvik Narayan Tiwari, Vallabhaneni Srikanth. (2026). Phage therapy in combating antimicrobial resistance: a one health approach. Vet Farm Frontier, 03(05), 19–24. https://doi.org/10.5281/zenodo.20686692