DOI:
https://doi.org/10.61900/SPJVS.2025.04.17

BACTERIOPHAGES IN VETERINARY MEDICINE: A REVIEW OF THERAPEUTIC APPLICATIONS, EVOLUTIONARY DYNAMICS, AND TRANSLATIONAL CHALLENGES

Dragoș Constantin ANIȚĂ[1], Adriana Elena ANIȚĂ[1]

e-mail: **dragos.anita@iuls.ro**

Abstract
The accelerating global burden of antimicrobial resistance (AMR) has intensified the need for novel antimicrobial strategies in both human and veterinary medicine. Bacteriophage therapy (BT), which utilizes lytic viruses that selectively target bacterial pathogens, is re-emerging as a biologically precise and ecologically compatible alternative to antibiotics. This review synthesizes current knowledge on phage biology, host-pathogen evolutionary dynamics, and veterinary applications across livestock, poultry, companion animals, and aquaculture. It further examines molecular innovations such as engineered phages, phage-derived enzymes (endolysins, depolymerases), and CRISPR-assisted genome editing. Documented experimental and clinical evidence, including recent case reports and trials, demonstrates significant phage activity against critical pathogens like *Staphylococcus aureus/pseudintermedius, Escherichia coli, Salmonella spp., Campylobacter spp., Klebsiella pneumoniae,* and *Pseudomonas aeruginosa*. Despite striking therapeutic potential, challenges persist, including the emergence of phage-resistant bacterial variants, complex regulatory constraints, variability in delivery systems, and the need for standardized manufacturing. Addressing these limitations through robust experimental design, enhanced regulatory frameworks (including magistral preparation models), and integration of advanced phage engineering tools will be critical for the full translational implementation of phage therapy under the *One Health* framework.

HISTORICAL TRAJECTORY AND ONE HEALTH RELEVANCE

Bacteriophages were independently identified in the early 20th century by Frederick Twort (1915) and Félix d'Herelle (1917), who not only demonstrated their lytic capacity but also successfully applied them to prevent *Salmonella gallinarum* infections in poultry, marking the first veterinary application (McAuliffe et al., 2007). Early veterinary phage applications expanded to include treatments targeting *Staphylococcus*, *E. coli*, and *Salmonella* infections in livestock (Barrow et al., 1998). However, with the advent of broad-spectrum antibiotics in the 1940s, phage therapy declined in Western practice due to inconsistent preparation methods, limited understanding of phage biology, and the overwhelming success of antibiotics. Conversely, Eastern European institutes, most notably the Eliava Institute in Georgia, continued systematic development of phage-based therapeutics. A renewed interest in Western science was triggered in the 1980s, particularly through the work of a research group that demonstrated that a single intraperitoneal injection could save bacteremic mice infected with *E. coli* or *S. enterica* serovar *Typhimurium* (Merril et al., 1996). The same team later showed, in a more recent study, that a lytic phage targeting vancomycin-resistant *Enterococcus faecium* (VRE) was effective in a mouse model (Biswas et al., 2002). A single intraperitoneal injection was sufficient to treat all of the VRE-bacteremic mice. Today, the growing AMR crisis, combined with consumer pressure to reduce antibiotic use in food-producing animals, has stimulated intense re-evaluation of phages as

[1] Ion Ionescu de la Brad" University for Life Sciences, Iași, Romania

precision antimicrobials (Kortright et al., 2019). Veterinary medicine plays a pivotal role in AMR dynamics, as resistant bacterial strains readily circulate between animals, humans, and the environment, forming a core pillar of One Health. Thus, bacteriophages offer a sustainable, species-targeted antimicrobial solution uniquely suited to integrated animal and public health strategies (Zhou et al., 2025).

Bacteriophage Biology: Structure, Replication, and Co-Evolution with Hosts

Bacteriophages are very diverse and play an important role in shaping microbial life. Their biology weaves together elegantly engineered structures, tightly orchestrated replication cycles, and a continual evolutionary arms race with their bacterial hosts.

Taxonomy and Morphology

The classification of bacteriophages is a constantly evolving field: over the decades, different classifications have succeeded one another. Initially based on viral morphology observed via electron microscopy and the type of nucleic acid, the current classification by the International Committee on Taxonomy of Viruses (ICTV) is based on their genomic proximity. Most identified therapeutic bacteriophages belong to the order *Caudovirales* characterized by their tailed morphology (Segundo-Arizmendi et al., 2025). Recent taxonomic revisions have introduced new genera, such as *Fibralongavirus* within *Siphoviridae*, identified in phages targeting canine pathogen *Staphylococcus pseudintermedius* (Zeman et al., 2019). The genetic material of bacteriophages is composed of either DNA or RNA, which can be double-stranded or single-stranded.

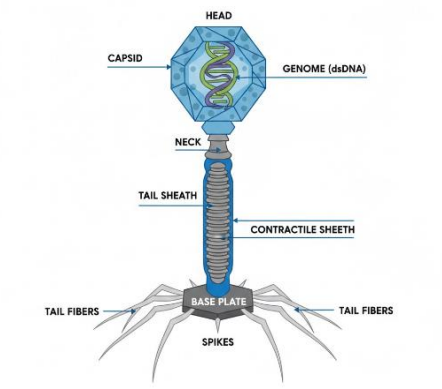

Fig. 1. Morphology af myovirus

This genetic material is packaged within a capsid of variable structure: polyhedral, filamentous, pleomorphic, or linked to a tail. Their distinct tail architectures, including receptor-binding proteins (RBPs) on fibers or baseplates, are critical for host interaction and specificity (Hrebík et al., 2019; Bardy et al., 2020). According to the size and contractile nature of the tail, three important families were described: *Podoviridae* (short, non-contractile tail), *Myoviridae* (long, contractile tail), and *Siphoviridae* (long, flexible, and non-contractile tail (Figure 1). Transmission Electron Microscopy (TEM) remains indispensable for morphological characterization, enabling differentiation between virulent (lytic) and temperate phages - a crucial step in pre-therapeutic development.

Replication Cycles: Lytic vs. Lysogenic Strategies

Phages are obligate intracellular parasites that rely on prokaryotic host machinery for replication, rendering them harmless to eukaryotic organisms. These viruses inhabit every ecosystem where bacteria are present, including sewage, fresh water, soil, and the human microbiome (Breitbart, 2012). Depending on their preferred life cycle, b. cteriophages are divided into virulent, temperate and chronic phages. Phages exhibit two primary replication strategies defining their therapeutic suitability. Lytic (virulent) phages follow a cycle of adsorption, genome injection, replication, assembly, and ultimately host cell lysis to release progeny virions. This lethal outcome makes them exclusively suitable for therapeutic use. In contrast, temperate phages can integrate their genome into the host chromosome as a prophage, replicating passively with the bacterium in a lysogenic state. This poses risks of horizontal gene transfer, including virulence or antibiotic resistance genes, rendering them unsuitable for therapy unless genetically modified into obligately lytic variants (Pires et al., 2016). These prophages, through their stable integration into the bacterial network, can also influence the metabolism and adaptation of the host to a changing environment (Wahl et al., 2019). It is important to note that once

integrated into the cellular genome, the viral genes are also capable of self-regulation via the expression of proteins that control the stability of the prophage within the chromosome. The study of these diverse genetic interactions represents a significant public health challenge because the bacteriophages present in the gut have a considerable impact on the microbiota.

Host Specificity and Evolutionary Adaptation (Arms Race)

Phage specificity is often strain-specific, mediated by RBPs that recognize bacterial surface structures like lipopolysaccharides, porins, pili, or capsule polysaccharides. This intimate interaction drives a relentless co-evolutionary arms race (Chen et al., 2024). Bacteria evolve resistance through diverse mechanisms: receptor modification or loss, activation of Restriction-Modification systems, Abortive Infection (Abi) systems, or CRISPR-Cas adaptive immunity. In response, therapeutic strategies must evolve, necessitating the use of well-characterized phage cocktails targeting multiple bacterial receptors, periodic phage library updates, or the deployment of genetically engineered phages with broadened host ranges to counteract resistance and maintain long-term efficacy.

Veterinary Applications of Phage Therapy: From Farm to Companion Animal

Phage therapy in veterinary medicine spans pre-harvest interventions (treating live animals to improve health and reduce zoonotic pathogens) and post-harvest applications (decontaminating food products).

3.1. Ruminants and Swine

In cattle, a primary focus is reducing the carriage of zoonotic pathogens like E. coli O157:H7 and Salmonella spp. Oral administration of encapsulated phage cocktails has demonstrated significant reductions in fecal shedding, though efficacy can be variable due to challenges of phage survival and activity in the complex gastrointestinal environment. In swine, prophylactic application of phage cocktails via feed or water has shown promise in reducing Salmonella colonization in piglets, thereby improving animal welfare and reducing contamination risk. Recent isolations of novel *Epseptimavirus* phages specific to *Salmonella enterica* and *E. coli* from environmental samples highlight the ongoing discovery of potential therapeutic agents (Cortes-Ortega et al., 2024; Zheng et al., 2024).

3.2. Poultry

Poultry are major reservoirs for foodborne pathogens *Campylobacter jejuni* and *Salmonella Enteritidis*. Phage therapy applied through feed, water, or oral gavage aims to reduce caecal colonization pre-slaughter. Studies have documented 2–3 $\log_{10}$ reductions in *Campylobacter* loads, directly supporting pre-harvest food safety applications. The success hinges on using cocktails effective against prevalent strains and timing administration close to slaughter.

3.3. Companion Animals

Phage therapy is gaining traction in small animal medicine for chronic, antibiotic-resistant infections. A key target is *Staphylococcus pseudintermedius* (MRSP), a leading cause of canine pyoderma, otitis, and wound infections. Phages from genera like *Kayvirus (Myoviridae)* and *Fibralongavirus (Siphoviridae)* show potent activity against MRSP (Zeman et al., 2019). Beyond dermatology, compassionate-use cases report successful outcomes in challenging scenarios: treatment of prosthetic joint infections (Tkhilaishvili et al., 2019; Ferry et al., 2021), chronic urinary tract infections (Kuipers et al., 2019), and infected wounds (Patel et al., 2021), often after antibiotic failure. These align with human medicine case reports detailing phage therapy for osteomyelitis (Fish et al., 2018; Clarke et al., 2020), diabetic foot ulcers (Duplessis & Biswas, 2020), and device-related infections (Exarchos et al., 2020; Mulzer et al., 2020).

3.4.Aquaculture

The intensive nature of aquaculture makes it highly vulnerable to bacterial diseases like vibriosis and aeromoniasis. Phage therapy offers an environmentally friendly alternative. Immersion (bath) treatments with phages specific to *Aeromonas hydrophila* or *Vibrio harveyi* have significantly reduced mortality in fish and shrimp. For instance, the novel phage AhyVDH1 exhibits strong lytic activity against *A. hydrophila* (Cheng et al., 2021).

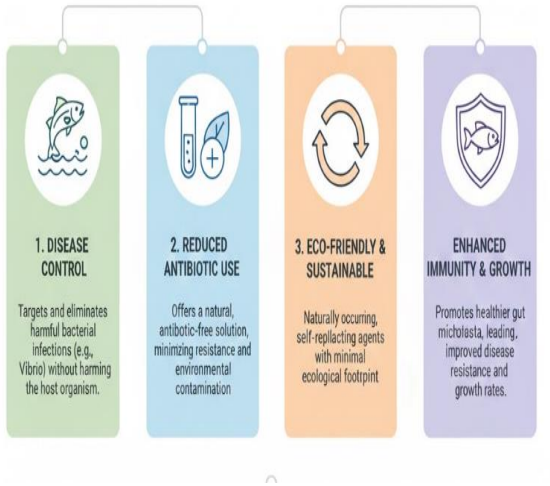

Figure 2. Advantages of phages in aquaculture

Field trials in shrimp culture demonstrate that phage treatment can achieve superior outcomes compared to antibiotics in controlling outbreaks, highlighting its practical scalability (Mazumder, 2022).

Phage therapy offers significant advantages over traditional antibiotic use in aquaculture, primarily because of its self-regulating and highly specific nature, making it a more environmentally sound and cost-effective approach to disease control (Figure 2). The key benefits include self-replication, where phages multiply only in the presence of target bacteria, allowing for smaller, cheaper initial doses, and auto-dosing, a mechanism ensuring phages naturally disappear once the pathogenic bacteria are eliminated, preventing the persistence of residues. Furthermore, phages possess a narrow action spectrum and high strain specificity, meaning they do not interfere with beneficial non-target bacteria or the host's body cells, thereby avoiding the broad ecological disruption caused by antibiotics; while this specificity can be a disadvantage, it is mitigated by using bacteriophage cocktails.

Confronting Biofilms: A Key Arena for Phage Therapy

Biofilms, structured communities encased in an extracellular polymeric substance (EPS), are a hallmark of chronic veterinary infections (e.g., otitis, wound infections, implant-associated infections) and confer extreme antibiotic tolerance. Beyond safety, phages are more environmentally friendly, are effective at clearing problematic biofilms, and, due to their short development cycles, are low-cost and easy to use and store, collectively positioning them as a robust, practical alternative for sustainable farming.

Phages combat biofilms through dual strategies: direct infection and lysis of metabolically active bacteria within the biofilm, and production of depolymerase enzymes that enzymatically degrade the EPS matrix, facilitating phage penetration and disrupting biofilm integrity (Kolenda, 2019). This anti-biofilm activity is particularly relevant for pathogens like *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*. For example, phages with depolymerase activity have proven effective against K. pneumoniae biofilms (Zurabov et al., 2023). However, phage therapy can sometimes paradoxically stimulate biofilm formation by selecting for mucoid or aggregation-prone mutants, underscoring the need for careful phage selection and combination strategies, such as phage-antibiotic synergy (PAS), which can enhance biofilm eradication (Diallo & Dublanchet, 2022).

The Rise of Phage Engineering and Enzybiotics

- **Engineered and Genomically Enhanced Phages**

Phage display technology is a versatile engineering platform used to select high-affinity binders and create functionalized phages. The technique, which earned George P. Smith and Sir Gregory P. Winter the 2018 Nobel Prize in Chemistry, works by genetically modifying phages to display peptides or proteins on their coat proteins. These engineered phages are then screened against a target to identify and select the molecules with the strongest binding affinity (Jaroszewicz et al., 2022). Advances in synthetic biology allow for the precise modification of phages to enhance therapeutic properties. CRISPR-Cas systems can be used to convert temperate phages into obligately lytic variants or to edit phage genomes to broaden host range, enhance lytic activity, or remove undesirable genes. Phage rebooting techniques enable the insertion of therapeutic cargo, such as biofilm-degrading enzymes or antimicrobial peptides, creating targeted delivery vehicles (Pires et al., 2016). The isolation and genomic characterization of novel phages, such as the *Klebsiella* phage EKq1, provide the raw material for these engineering platforms (Anderson et al., 2024).

- **Enzybiotics: Endolysins and Depolymerases**

  Phage-derived enzymes, or enzybiotics, offer a distinct therapeutic approach. Endolysins are peptidoglycan hydrolases produced by phages to lyse the bacterial cell wall from within during the lytic cycle. When applied exogenously as purified recombinant proteins, they cause rapid osmotic lysis of Gram-positive bacteria like Staphylococcus, even against antibiotic-resistant strains. Depolymerases, as previously noted, target capsules, slime layers, or EPS. These enzymes are not self-replicating, potentially simplifying regulatory pathways, and can be used synergistically with phages or conventional antibiotics to enhance efficacy and prevent resistance.

- **Targeting Critical Pathogens: Documented Evidence**

  Klebsiella pneumoniae: The rapid spread of carbapenem-resistant *K. pneumoniae* (CRKP) has made it a prime target. Studies report the isolation of novel, potent phages against CRKP strains, including those from ventilator-associated pneumonia in COVID-19 patients (Mohammadi et al., 2023).

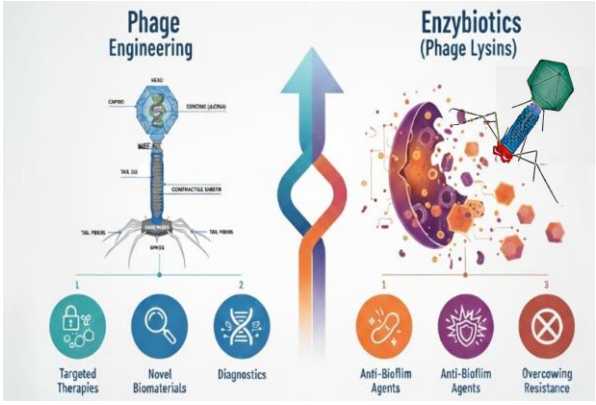

Fig3. Phage Engineering and Enzybiotics

- Phage cocktails have demonstrated efficacy against extensively drug-resistant sequence types (Martins et al., 2022), and case reports show successful personalized phage therapy, noting that phage resistance development can sometimes be associated with reduced bacterial virulence (Li et al., 2023; Abbas et al., 2025; Duarte et al., 2024).
  - *Pseudomonas aeruginosa*: A major cause of chronic otitis and wound infections in animals. Human medicine trials and case reports, such as the PhagoBurn trial for burn wounds (Jault et al., 2019) and treatment of respiratory infections in cystic fibrosis patients (Law et al., 2019), provide a robust proof-of-concept for veterinary translation.
  - *Staphylococcus aureus*: Phage therapy has been used safely and effectively in human trials for conditions like chronic rhinosinusitis (Ooi et al., 2019) and severe systemic infections

(Fabijan et al., 2020), supporting its potential for analogous *S. pseudintermedius* infections in dogs.

- *Aeromonas hydrophila* and *Salmonella spp*.: As noted in aquaculture and livestock sections, multiple phages with therapeutic potential have been isolated and characterized (Cheng et al., 2021; Cortes-Ortega et al., 2024).

- Targeting intracellular bacterial pathogens like *Mycobacteria and Mycoplasma* is challenging because they are shielded from traditional antibiotics and immune responses, often using host cells as "Trojan horses" for dissemination. While bacteriophages (phages) can naturally enter mammalian cells, they often fail to reach the same internal compartments as the bacteria, limiting their efficacy. To overcome this, molecular engineering is used to modify phages, for example, by adding cell-penetrating or receptor-binding peptides, to enhance their uptake and direct them to specific intracellular locations, showing promise in killing pathogens like *Clamydia trachomatis, E. coli, and Salmonella sp. (*Zhao et al., 2023*)*. A major hurdle remains the diversity of intracellular niches (cytosol, phagosomes, etc.) occupied by different pathogens.

Regulatory Landscape and Translational Barriers

Phage display's utility extends significantly beyond simple molecule discovery, acting as a new enabling technology across several biomedical fields. Specifically, it supports the creation of highly sensitive diagnostic assays and the efficient screening for ligands targeting disease biomarkers. This versatile platform has found broad application in the discovery and engineering of therapeutic antibodies (Zhang, 2023), the development of systems for targeted drug delivery (André et al., 2022) to increase treatment efficacy, and the innovative field of biomaterials engineering (Davidson et al., 2020). Phages present a unique regulatory challenge as dynamic, self-replicating biological entities, not static chemical drugs. In the European Union, they are typically regulated as Biological Medicinal Products, requiring full Good Manufacturing Practice (GMP) compliance and extensive clinical trial data—a costly and lengthy process ill-suited for personalized or rapidly adaptable therapies. Innovative regulatory models are emerging. Belgium has formalized a magistral preparation framework, allowing customized phage preparations to be compounded in hospital pharmacies for specific patients under medical responsibility (Pirnay et al., 2018). Other proposals include adopting multi-strain dossiers (similar to vaccines) and establishing centralized phage banks with pre-characterized, quality-controlled phages to streamline access.

Key translational barriers include:

- Pharmacokinetics/Pharmacodynamics (PK/PD): Understanding phage distribution, persistence, and replication dynamics in vivo across different species and routes of administration (oral, topical, systemic).
- Standardization: Developing universal potency assays, stability testing protocols, and purity criteria (e.g., ensuring removal of bacterial endotoxins and exclusion of temperate phages).
- Manufacturing: Scaling up production under GMP while maintaining phage activity and stability, especially for cocktails.
- Resistance Monitoring: Implementing surveillance for phage-resistant bacterial variants during therapy.

Future Perspectives and Integration into *One Health* perspective

The future of veterinary phage therapy depends on strategic integration:

- Building Phage Biobanks: Establishing international, curated collections of genomically sequenced lytic phages against priority veterinary pathogens to enable rapid matching to clinical isolates.

- Advanced Delivery Systems: Research into microencapsulation for oral delivery, stable topical formulations, and inhaled phages for respiratory infections.
- Definitive Clinical Trials: Conducting large-scale, randomized controlled trials in target animal species to generate the robust efficacy and safety data required for wider regulatory approval and veterinary practitioner acceptance.
- Synergistic Combinations: Systematically exploring Phage-Antibiotic Synergy (PAS) and phage-enzybiotic combinations to enhance efficacy, reduce resistance emergence, and treat biofilm-associated and intracellular infections (Fajardo-Lubian & Venturini, 2023).
- One Health Surveillance: Integrating phage therapy into AMR surveillance networks, using phages not only as therapeutics but also as precise diagnostic and typing tools to track resistant bacterial clones across human, animal, and environmental reservoirs.

CONCLUSION

Bacteriophage therapy represents a powerful, evolutionarily informed alternative to antibiotics in veterinary medicine. Its high specificity, capacity for self-replication at the infection site, ability to disrupt biofilms, and potential for genetic engineering make it a uniquely adaptable tool. While substantial challenges in regulation, standardization, and delivery persist, the growing body of successful experimental studies, compassionate-use cases in both human and veterinary medicine, and continuous scientific innovation are paving a credible translational pathway. By addressing these challenges through collaborative research, flexible regulation, and *One Health* integration, phage therapy can evolve into a mainstream, sustainable modality for combating infectious diseases in animals, ultimately contributing to global AMR mitigation and improved ecosystem health.

REFERENCES

Abbas S, Kanwar R, Ullah K, et al. Bacteriophage therapy: a possible alternative therapy against antibiotic-resistant strains of Klebsiella pneumoniae. *Front Microbiol*. **2025**; 16:1443430. doi:10.3389/fmicb.2025.1443430

André, A. S., Moutinho, I., Dias, J. N. R. and Aires-da-Silva, F. (2022). In vivo phage display: a promising selection strategy for the improvement of antibody targeting and drug delivery properties. *Front. Microbiol*. 13, 962124. https://doi.org/10.3389/fmicb.2022.962124

Bird JT, Burke KA, Urick CD, et al. Genome sequence of the Klebsiella quasipneumoniae bacteriophage EKq1 with activity against Klebsiella pneumoniae. *Microbiol Resour Announc*. **2024**;13(1):e0095423. doi:10.1128/MRA.00954-23

Bárdy P, Füzik T, Hrebík D, Pantůček R, Beatty JT, Plevka P. Structure and mechanism of DNA delivery of a gene transfer agent. *Nat Commun.* **2020**;11(1):3034. doi:10.1038/s41467-020-16669-9

Barrow P, Lovell M, Berchieri A Jr. Use of lytic bacteriophage for control of experimental Escherichia coli septicemia and meningitis in chickens and calves. *Clin Diagn Lab Immunol*. **1998**;5(3):294-298. doi:10.1128/CDLI.5.3.294-298.1998

Barrow P, Lovell M, Berchieri A Jr. Use of lytic bacteriophage for control of experimental Escherichia coli septicemia and meningitis in chickens and calves. *Clin Diagn Lab Immunol.* **1998**;5(3):294-298. doi:10.1128/CDLI.5.3.294-298.1998

Biswas B, Adhya S, Washart P, et al. Bacteriophage therapy rescues mice bacteremic from a clinical isolate of vancomycin-resistant Enterococcus faecium. *Infect Immun.* **2002**;70(1):204-210. doi:10.1128/IAI.70.1.204-210.2002

Breitbart M. Marine viruses: truth or dare. *Annu Rev Mar Sci*. **2012**;4:425-448. doi:10.1146/annurev-marine-120709-142805

Chen L, Zhao X, Wongso S, Lin Z, Wang S. Trade-offs between receptor modification and fitness drive host-bacteriophage co-evolution leading to phage extinction or co-existence. *ISME J*. **2024**;18(1):wrae214.

Cheng Y, Gao D, Xia Y, et al. Characterization of novel bacteriophage AhyVDH1 and its lytic activity against Aeromonas hydrophila. *Curr Microbiol*. **2021**;78:329-337.

Clarke AL, De Soir S, Jones JD. The safety and efficacy of phage therapy for bone and joint infections: a systematic review. *Antibiotics*. **2020**;9(11):795.

Cortes-Ortega E, Hansen EG, Iskender I, et al. Isolation and characterization of Salmonella enterica- and Escherichia coli-specific bacteriophages of the genus Epseptimavirus from wastewater in Minnesota. *Arch Virol*. **2024**;169(11):255.

Davidson T.A., McGoldrick S.J., Kohn D.H. Phage display to augment biomaterial function. **2020**, *Int. J. Mol. Sci.* 21, 5994. https://doi.org/10.3390/ijms21175994

Duarte J, Máximo C, Costa P, et al. Potential of an isolated bacteriophage to inactivate Klebsiella pneumoniae: preliminary studies to control urinary tract infections. *Antibiotics*. **2024**;13(2):195.

Duplessis CA, Biswas B. A review of topical phage therapy for chronically infected wounds and preparations for a randomized adaptive clinical trial evaluating topical phage therapy in chronically infected diabetic foot ulcers. *Antibiotics*. **2020**;9(7):377.

Exarchos V, Tkhilaishvili T, Potapov E, et al. Successful bacteriophage treatment of infection involving cardiac implantable electronic device and aortic graft: a Trojan horse concept. *Europace*. **2020**;22(4):597.

Fabijan AP, Lin RCY, Ben Zakour NL, et al. Safety of bacteriophage therapy in severe Staphylococcus aureus infection. *Nat Microbiol*. **2020**;5:465–472.

Fajardo-Lubian A, Venturini C. Use of bacteriophages to target intracellular pathogens. *Clin Infect Dis.* **2023**;77(suppl 5):S423–S432.

Ferry T, Kolenda C, Batailler C, et al. Case report: arthroscopic “debridement antibiotics and implant retention” with local injection of personalized phage therapy to salvage a relapsing Pseudomonas aeruginosa prosthetic knee infection. *Front Med (Lausanne)*. **2021**;8:569159.

Fish R, Kutter E, Bryan D, Wheat G, Kuhl S. Resolving digital staphylococcal osteomyelitis using bacteriophage—a case report. *Antibiotics*. **2018**;7(4):87.

Hrebík D, Štveráková D, Škubník K, et al. Structure and genome ejection mechanism of Staphylococcus aureus phage P68. *Sci Adv*. ***2019***;5(10):eaaw7414.

Jaroszewicz W, Morcinek-Orłowska J, Pierzynowska K, Gaffke L., Węgrzyn, G. Phage display and other peptide display technologies. **2022**, *FEMS Microbiol*. Rev. 46, https://doi.org/10.1093/femsre/fuab052

Jault P, Leclerc T, Jennes S, et al. Efficacy and tolerability of a cocktail of bacteriophages to treat burn wounds infected by Pseudomonas aeruginosa (PhagoBurn): a randomised, controlled, double-blind phase 1/2 trial. *Lancet Infect Dis*. **2019**;19(1):35-45.

Kolenda C. Phagothérapie et Infections Ostéo-Articulaires: Évaluation de L’activité Antibiofilm et Antibactérienne Intracellulaire D’un Assemblage de Trois Bactériophages Anti-Staphylococcus aureus [dissertation]. Lyon, France: Université Claude Bernard Lyon 1; **2019**.

Kortright KE, Chan BK, Koff JL, Turner PE. Phage therapy: a renewed approach to combat antibiotic-resistant bacteria. *Cell Host Microbe*. **2019**;25(2):219-232.

Kuipers S, Ruth MM, Mientjes M, de Sévaux RG, van Ingen J. A Dutch case report of successful treatment of chronic relapsing urinary tract infection with bacteriophages in a renal transplant recipient. *Antimicrob Agents Chemother*. **2019**;64(1):e01281-19.

Law N, Logan C, Yung G, et al. Successful adjunctive use of bacteriophage therapy for treatment of multidrug-resistant Pseudomonas aeruginosa infection in a cystic fibrosis patient. *Infection*. **2019**;47(4):665–668.

Li J, Yan B, He B, et al. Development of phage resistance in multidrug-resistant Klebsiella pneumoniae is associated with reduced virulence: a case report of a personalised phage therapy. *Clin Microbiol Infect*. **2023**;29(12):1601.e1-1601.e5.

Martins WM, Li M, Sands K, et al. Effective phage cocktail to combat the rising incidence of extensively drug-resistant Klebsiella pneumoniae sequence type 16. *Emerg Microbes Infect*. **2022**;11(1):1015-1023.

Mazumder F. Isolation, Characterisation and Preservation of Bacteriophages for Use in Treatment of Aeromonas hydrophila Infection in Finfish [dissertation]. Adelaide, Australia: University of Adelaide; **2022**.

Merril CR, Biswas B, Carlton R, et al. Long-circulating bacteriophage as antibacterial agents. *Proc Natl Acad Sci U S A*. **1996**;93(8):3188-3192. doi:10.1073/pnas.93.8.3188

Mohammadi M, Saffari M, Siadat SD, et al. Isolation, characterization, therapeutic potency, and genomic analysis of a novel bacteriophage vB_KshKPC-M against carbapenemase-producing Klebsiella pneumoniae strains (CRKP) isolated from ventilator-associated pneumoniae (VAP) infection of COVID-19 patients. *Ann Clin Microbiol Antimicrob*. **2023**;22(1):18.

Mulzer J, Trampuz A, Potapov EV. Treatment of chronic left ventricular assist device infection with local application of bacteriophages. *Eur J Cardiothorac Surg*. **2020**;57(5):1003-1004.

Ooi ML, Drilling AJ, Morales S, et al. Safety and tolerability of bacteriophage therapy for chronic rhinosinusitis due to Staphylococcus aureus. *JAMA Otolaryngol Head Neck Surg*. **2019**;145(8):723-729.

Patel DR, Bhartiya SK, Kumar R, Shukla V, Nath G. Use of customized bacteriophages in the treatment of chronic nonhealing wounds: a prospective study. *Int J Low Extrem Wounds*. **2021**;20(1):37-46.

Pires DP, Cleto S, Sillankorva S, Azeredo J, Lu TK. Genetically engineered phages: a review of advances over the last decade. *Microbiol Mol Biol Rev*. **2016**;80(3):523-543.

Pirnay JP, Verbeken G, Ceyssens PJ, et al. The magistral phage. *Viruses*. **2018**;10(2):64.

Segundo-Arizmendi N, Arellano-Maciel D, Rivera-Ramírez A, et al. Bacteriophages: a challenge for antimicrobial therapy. *Microorganisms*. **2025**;13(1):100.

Tkhilaishvili T, Winkler T, Müller M, Perka C, Trampuz A. Bacteriophages as adjuvant to antibiotics for the treatment of periprosthetic joint infection caused by multidrug-resistant Pseudomonas aeruginosa. *Antimicrob Agents Chemother*. **2019**;64(1):e00924-19.

Zeman M, Bárdy P, Vrbovská V, et al. New genus Fibralongavirus in Siphoviridae phages of Staphylococcus pseudintermedius. *Viruses.* **2019**;11(12):1143.

Zhang Y. Evolution of phage display libraries for therapeutic antibody discovery. **2023**, *MAbs* 15, 2213793. https://doi.org/10.1080/19420862.2023.2213793.

Zhao M, Tan X, Liu Z, Dou L, Liu D, Pan Y, Ma Y, Yu J. Engineered phage with cell-penetrating peptides for intracellular bacterial infections. **2023**, *mSystems* 8, e00646-e00623. https://doi.org/10.1128/msystems.00646-23

Zheng X, Wang X, Zhou Y, et al. Isolation, whole genome sequencing and application of a broad-spectrum Salmonella phage. *Arch Microbiol*. **2024**;206(8):335.

Zhou Y, Yang H, Wang S. Editorial: Bacteriophages, a weapon against animal bacterial pathogens and biofilms. *Front Vet Sci.* **2025**; 12:1625678.

Zurabov F, Glazunov E, Kochetova T, Uskevich V, Popova V. Bacteriophages with depolymerase activity in the control of antibiotic resistant Klebsiella pneumoniae biofilms. *Sci Rep*. **2023**;13(1):15188.