Review Article

Bacteriophage Therapy in Aquaculture: A Sustainable Antibacterial Strategy Supporting the One Health Approach

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Abstract

Aquaculture has become one of the fastest-growing food sectors globally, but its expansion is increasingly challenged by bacterial disease outbreaks and the rising threat of antimicrobial resistance (AMR). As conventional antibiotic treatments lose effectiveness, bacteriophage therapy – the use of viruses that selectively infect and lyse bacteria – has emerged as a promising alternative. Phages offer high specificity, minimal environmental impact, and proven efficacy against multidrug-resistant pathogens. This review provides an updated synthesis of current knowledge on the application of bacteriophages and phage-derived products, such as lysins and tail-like bacteriocins, in aquaculture systems. We explore their mechanisms of action, therapeutic advantages, and outcomes from experimental and field trials against key pathogens, including *Aeromonas hydrophila*, *Vibrio harveyi*, *Edwardsiella tarda*, and *Streptococcus iniae*. Importantly, phage therapy aligns with the One Health framework, which emphasizes the interdependence of human, animal, and environmental health. By reducing the use of antibiotics in aquatic farming, phage applications can help curb the spread of AMR, protect water ecosystems, and enhance food safety. Despite its potential, challenges such as phage resistance, endotoxin release, intracellular pathogen targeting, and standardization gaps must be addressed for broader adoption. We conclude by outlining future research priorities, including genome-guided phage selection, optimized delivery systems, and the need for standardized efficacy testing. Phage therapy thus represents a sustainable and integrative approach to aquatic disease management and global public health.

Keywords: Antimicrobial resistance, aquaculture, bacteriophage therapy, fish pathogens, lytic phages, one health approach, phage resistance, phage-derived enzymes

Introduction

Aquaculture, the cultivation of aquatic animals and plants across freshwater, brackish, and marine systems, has emerged as a key pillar of sustainable global food production (1). Driven by rapid population growth and the escalating demand for seafood, aquaculture now contributes nearly one-third of the world's seafood supply and is widely recognized as one of the most dynamic and rapidly advancing food-producing sectors (2). In India, aquaculture has undergone remarkable expansion and diversification in recent decades, placing the country as the world's second-largest aquaculture producer after China (3). This sector provides direct and indirect livelihoods for more than 14.5 million people and contributed approximately USD 4.7 billion in foreign exchange earnings during the 2015–2016 fiscal year (4).

Despite these advances, the aquaculture industry remains vulnerable to infectious diseases, which continue to pose serious threats to productivity and economic viability. A wide range of microbial agents – including bacteria, viruses, protists, helminths, and fungi – are responsible for these disease outbreaks, with bacterial infections accounting for the majority of losses across fish and shellfish operations (5-7). Pathogenic bacteria affecting aquaculture can be broadly classified into two groups: Indigenous microflora, such as *Photobacterium damselae*, *Vibrio anguillarum*, *Vibrio vulnificus*, *Aeromonas hydrophila*, and *Aeromonas salmonicida*, which naturally inhabit aquatic environments; and exogenous microflora,

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including enteric bacteria like *Salmonella* spp. and *Escherichia coli*, typically introduced via anthropogenic contamination from livestock and human waste (8-11).

Among bacterial diseases, vibriosis and photobacteriosis (previously known as pasteurellosis) are of particular concern, as they frequently lead to high mortality rates in cultured fish. These diseases are primarily caused by members of the *Vibrionaceae* family, including pathogenic species such as *V. anguillarum*, *V. vulnificus*, *V. parahaemolyticus*, and *P. damselae* subspecies *piscicida* and *damselae*. These pathogens are known for their broad host range and virulence in diverse fish species (12,13).

Conventionally, antibiotics have been used to manage bacterial infections in aquaculture, particularly for conditions such as epizootic ulcerative syndrome, skin and gill lesions, tail rot, and fin erosion. While initially effective and relatively affordable, this strategy is now limited by the widespread emergence of multidrug-resistant (MDR) bacteria (14). In addition, antibiotic use carries the risk of ecological imbalance, residual contamination in aquatic environments and seafood, and adverse public health consequences.

In recent years, bacteriophages – viruses that specifically infect and lyse bacteria – have re-emerged as a promising alternative to conventional antibiotics in aquaculture. Phages are naturally occurring, highly specific, and environmentally benign. Their ability to selectively target bacterial pathogens without disturbing beneficial microbiota or the surrounding ecosystem makes them particularly suitable for aquaculture settings. Phage therapy, first introduced by Félix d'Herelle in the early 20th century, has found renewed relevance in controlling antibiotic-resistant pathogens in fish farming operations (15). In many instances, the success of phage application has been attributed to their environmental adaptability and the close interaction between phage and host within aquatic systems.

Despite this growing interest, comprehensive reviews detailing the applications, mechanisms, limitations, and future potential of phage therapy in aquaculture remain limited. This article aims to provide an updated overview of bacteriophage-based interventions in aquaculture, with a focus on their therapeutic potential, mechanistic basis, advantages over conventional approaches, and the emerging challenges that need to be addressed for broader adoption. Additionally, the review explores how phage therapy supports the One Health framework, which emphasizes the interconnectedness of human, animal, and environmental health. By reducing the reliance on antibiotics in aquaculture systems, phage therapy can help curb the spread of antimicrobial resistance (AMR), protect aquatic ecosystems from pharmaceutical residues, and safeguard public health – positioning it not only as a promising therapeutic tool, but also as a vital component of integrated health strategies across ecosystems.

Advantages of Phage Therapy

Phage therapy offers several compelling advantages over traditional antibiotic treatments, particularly in the context of MDR bacterial infections common in aquaculture environments:

1. Efficacy against MDR pathogens: Unlike antibiotics, which often fail against resistant strains, phages employ unique mechanisms – such as targeted lysis – to effectively eliminate MDR bacteria.
2. High specificity: Phages exhibit precise host specificity, targeting only the intended pathogenic bacteria while leaving beneficial microflora intact. This reduces the risk of dysbiosis or unintended microbial shifts.
3. Adaptability: Phages can evolve alongside bacteria, allowing for dynamic responses to the emergence of phage-resistant strains.
4. Cost-effectiveness: The development and production of phage preparations are generally less expensive and faster than the discovery and approval of new antibiotics.
5. Host safety: As phages do not infect eukaryotic cells and do not interfere with host metabolism, they are associated with minimal side effects, making them a safe therapeutic option in aquaculture settings.

Mechanism of Bacterial Lysis by Phages

The phage life cycle begins with the adsorption of the virus to a specific receptor on the surface of the bacterial host. These receptors are often composed of proteins, polysaccharides, or lipopolysaccharides. Most phages exhibit a high degree of host specificity, typically infecting only particular bacterial species or strains; however, polyvalent phages capable of infecting multiple strains or closely related species are well documented and occur with notable frequency, particularly among members of the Myoviridae family.

Once attached, the phage injects its nucleic acid into the bacterial cytoplasm. The early phase of infection involves the expression of genes that suppress host bacterial functions. This is followed by replication of the phage genome and synthesis of structural proteins. Assembly of the viral components – capsid, tail, and genomic packaging – occurs next, culminating in the release of progeny phages via host cell lysis.

The lysis process is mediated by two essential proteins:

- Holin: Forms pores in the bacterial cell membrane.
- Endolysin (Lysin): A peptidoglycan-degrading enzyme that breaks down the bacterial cell wall.

This process allows phages to rapidly infect adjacent bacterial cells, making them highly effective for biocontrol. Notably, purified endolysins are also being explored as standalone antimicrobial agents.

Bacteriophage Receptors and Resistance Mechanisms

While phage therapy holds promise, the emergence of phage resistance is an important challenge. Bacteria can inhibit phage infection through various mechanisms, including:

1. Blocking adsorption: The most common resistance mechanism involves the loss, modification, or masking of phage receptors on the bacterial surface. Examples include altered outer membrane proteins like OmpA in *E. coli* or the masking effect of Protein A in *Staphylococcus aureus* (16,17).
2. Superinfection exclusion (Sie): Prevents the entry of phage DNA into already infected cells (18).
3. Restriction-modification and clustered regularly interspaced short palindromic repeats systems: These systems recognize and degrade foreign phage DNA (19).
4. Abortive infection systems (Abi): These act as a last-resort mechanism where the infected host cell sacrifices itself to prevent phage replication (20).

Some bacteria also employ phase variation, altering surface antigen expression to evade phage recognition. For instance, *Bordetella* spp. switch between Bvg + and Bvg– phases to change surface structures (21).

Importantly, resistance often comes at a cost. Loss of surface receptors may compromise bacterial fitness or attenuate virulence, thus enhancing the host's ability to clear the infection.

Prerequisites for Effective Phage Therapy

Successful implementation of phage therapy depends on meeting several key prerequisites:

1. Comprehensive understanding of phage biology: The specific interactions between phage and host bacteria must be well characterized before therapeutic use, including the infection dynamics and lifecycle.
2. Safety and purity of preparations: Phage formulations should be devoid of bacterial contaminants and endotoxins to prevent adverse reactions.
3. Stability and viability: Phage suspensions must be stable under storage and environmental conditions relevant to aquaculture.
4. Identification of phage receptors: Knowledge of the exact bacterial receptors ensures targeted therapy and anticipates potential resistance. In large bacterial populations (10^6–10^8 cells), spontaneous mutants lacking these receptors may arise. However, if the receptor plays a role in bacterial virulence (e.g., lipopolysaccharide [LPS]), its loss could attenuate the pathogen.
5. Preclinical testing: Phage efficacy and safety must be validated in appropriate animal models prior to widespread application, as *in vivo* behavior can differ significantly from *in vitro* observations.

As emphasized by Levin and Bull, the goal of phage therapy is not necessarily to sterilize the host environment but to reduce the bacterial load to levels manageable by the innate immune system (22).

Bacteriophage Therapy in Aquaculture

Bacteriophage therapy has been explored across multiple disciplines, including human and veterinary medicine, food safety, and agriculture. Its application in aquaculture, however, has gained significant momentum only in recent decades. The potential of phages for controlling fish pathogens was first acknowledged in 1981, and shortly thereafter, their therapeutic potential was demonstrated in Japanese eel (*Anguilla japonica*) (23). Subsequent studies laid the groundwork for *in vivo* experiments aimed at evaluating the clinical efficacy of phage treatments under aquaculture conditions.

A landmark study in 1997 confirmed the protective role of bacteriophages against *Lactococcus garvieae* infections in yellowtail (*Seriola quinqueradiata*) (11). At that time, although a vaccine for lactococcosis existed, resistant strains of *L. garvieae* and the lack of effective alternatives prompted exploration of phages. A virulent Siphoviridae phage, PLgY, was isolated from infected fish and shown to exert strong lytic activity (24). *L. garvieae* isolates from fish and aquaculture environments were grouped based on susceptibility to various phages, providing a foundation for targeted biocontrol (25).

Phage application in *Plecoglossus altivelis* (ayu fish) against *Pseudomonas plecoglossicida* – the causative agent of hemorrhagic ascites disease – also yielded promising outcomes. Notably, phage-enriched feed provided prophylactic protection, while direct water treatment helped suppress transmission. Importantly, no evidence of phage-resistant bacteria or neutralizing antibodies was detected, and the intervention significantly reduced infection incidence and fish mortality (26).

In an early effort to control *A. hydrophila*, a pathogen responsible for tail and fin rot and hemorrhagic septicemia in freshwater species, Hou *et al*. characterized eight phages (27). Among them, phage AH1 demonstrated potent lytic activity. Although not therapeutic when co-administered with bacteria, AH1 significantly reduced pathogen load when introduced into the water column, suggesting its efficacy as a preventive agent.

More recently, Jun *et al*. isolated two Myoviridae phages (pAh1-C and pAh6-C) targeting *A. hydrophila* and evaluated their efficacy in *Misgurnus anguillicaudatus* (loaches) (28). Administered either intraperitoneally or orally via phage-infused feed, both methods showed comparable effectiveness in reducing fish mortality. No adverse effects on fish health or behaviour were observed over a month-long trial. The study also recommended using phage combinations to enhance therapeutic efficiency.

Another notable study by Imbeault *et al*. demonstrated the efficacy of myovirus HER110 in treating *A. salmonicida* subsp.

salmonicida-induced furunculosis in brook trout (*Salvelinus fontinalis*) (29). The persistence of aeromonads in gravel biofilms within aquaria was noted as a challenge, potentially contributing to reinfection. The authors suggested using phage cocktails and higher multiplicities of infection (MOIs >1) to counteract resistant strains and improve outcomes.

Contrastingly, Verner-Jeffreys *et al*. reported limited success in using phages to treat furunculosis in rainbow trout (*Oncorhynchus mykiss*) and Atlantic salmon (*Salmo salar*) (30). Despite using three lytic phages under controlled conditions, mortality was only delayed – not prevented. The authors attributed the lack of success to the high infectivity of *A. salmonicida*, even at low inocula, and the rapid progression of the disease.

The therapeutic use of phages against *Edwardsiella tarda* – a pathogen responsible for enteric septicemia of catfish (ESC) – has also been explored. Hsu *et al*. reported a ~1-log CFU/mL reduction in *E. tarda* over 4–8 h at MOI = 1, while Wu and Chao demonstrated a ~3-log reduction in bacterial counts using phage ϕ Edwardsiella tarda (ET)-1, even at an MOI as low as 0.08 (31,32).

An Indian study by Prasad *et al*. documented the effective use of phages against *Flavobacterium columnare* in *Clarias batrachus* (catfish), a pathogen responsible for columnaris disease in numerous freshwater species (33). However, data on phage efficacy against *F. psychrophilum* – a major pathogen in rainbow trout and ayu – remain mixed. While Madsen *et al*. observed no significant improvement in survival, Sieiro *et al*. reported increased survival in phage-treated salmonids in Chile (34,35).

Phage therapy has also been studied against *Streptococcus iniae*, a zoonotic fish pathogen causing significant losses in tilapia, trout, salmon, and yellowtail. In Japanese flounder (*Paralichthys olivaceus*), Matsuoka *et al*. demonstrated reduced mortality following phage administration (36). Nonetheless, the emergence of phage-resistant *S. iniae* in some fish underscored the need for improved formulations and surveillance.

Vibrio harveyi, a naturally bioluminescent and highly virulent pathogen in marine invertebrates and finfish, causes luminous vibriosis – a disease of critical concern in shrimp hatcheries (37). Antibiotics have traditionally been employed to combat this pathogen, but resistance is increasingly common, compromising treatment efficacy. Multiple studies, including those by Karunasagar *et al*., have shown that phage therapy can reduce *V. harveyi* loads in hatchery waters by 2–3 log units (38). Phage Viha10, in particular, was found effective against biofilms, reducing bacterial concentration by 3 logs over 18 h. However, efficacy against crustaceans and molluscs such as pearl oysters and spiny lobsters has been inconsistent, and further studies are warranted.

Despite these promising results, phage therapy in aquaculture remains in its early stages. Limited success across a broad spectrum of hosts, inconsistent study designs, and variable environmental parameters highlight the need for more robust field trials. Future research should focus on expanding host coverage, standardizing treatment protocols, and developing phage formulations tailored to specific aquaculture systems.

Phage-Derived Products

Beyond whole-virus therapy, several purified bacteriophage-derived products have been developed and evaluated as anti-infective agents, particularly against Gram-positive pathogens. Among the most studied are phage lysins and tail-like bacteriocins (39).

Bacteriophage lysins are peptidoglycan-degrading enzymes capable of cleaving bacterial cell walls from the outside. They are especially effective against Gram-positive bacteria due to the exposed nature of their peptidoglycan layer. Unlike conventional antibiotics, which typically require actively dividing cells and intracellular access (e.g., β-lactams), lysins act rapidly – even on dormant or non-replicating bacterial cells – achieving bacteriolysis within seconds of application. When used in combination, lysins with complementary cleavage sites have shown synergistic effects.

Phage lysins are also relatively specific to target bacterial species, preserving commensal microbiota. However, their utility against Gram-negative bacteria remains limited, as their outer membrane prevents lysin penetration. Strategies such as lysin engineering, fusion with membrane-disruptive peptides, or co-administration with permeabilizers are currently under exploration to overcome this barrier.

Phage tail-like bacteriocins represent another category of promising antibacterial agents. These high molecular-weight protein complexes, produced by various Gram-negative bacteria (including members of *Enterobacteriaceae*), resemble the structural tails of bacteriophages (40,41). They exert their antimicrobial activity by forming pores in the bacterial cell envelope, leading to rapid ion loss and membrane disruption. These proteins, such as R-type pyocins in *Pseudomonas*, are being actively investigated as potential alternatives to whole phage particles for targeted pathogen control (42).

Together, these phage-derived agents offer refined tools for antimicrobial intervention, especially when whole phage therapy may be limited by resistance, regulatory, or formulation challenges.

Challenges in Phage Therapy

Despite its numerous advantages, phage therapy faces several scientific and practical challenges:

1. Emergence of phage resistance: Just as bacteria develop resistance to antibiotics, they can evolve mechanisms to evade phage infection. These include:
    - Alterations or masking of phage receptors
    - CRISPR-Cas-mediated immunity
    - Superinfection exclusion systems
    - Abortive infection mechanisms

However, unlike antibiotics, new phages can often be isolated from the environment to counter resistant strains, offering a naturally adaptive solution.

2. Host immune response and hypersensitivity: Although rarely observed, the administration of high phage titers may elicit immune responses, including the production of phage-neutralizing antibodies or, theoretically, hypersensitivity reactions such as anaphylaxis. Preclinical studies and dose optimization are thus critical to ensure safety.
3. Endotoxin release upon bacterial lysis: Phage-mediated lysis of Gram-negative bacteria can release LPS endotoxins, potentially triggering systemic inflammatory responses such as fever or septic shock – similar to what is observed with some antibiotics. Mitigation strategies include dose modulation or co-treatment with detoxifying agents.
4. Horizontal gene transfer risks: Lysogenic or temperate phages may inadvertently mediate the transfer of virulence factors or antibiotic resistance genes through generalized or specialized transduction. Well-documented cases include the cholera toxin bacteriophage (CTX)ϕ prophage enhancing *Vibrio cholerae* virulence (43). To prevent such outcomes, only strictly lytic phages with fully sequenced genomes and no known integrase or toxin genes should be selected for therapy.
5. Limited efficacy against intracellular pathogens: Phages are typically ineffective against intracellular bacterial pathogens such as *Salmonella* spp., which can survive and replicate within host cells, particularly macrophages, thereby evading direct phage access due to the inability of phages to penetrate eukaryotic cell membranes. While this intracellular niche limits the therapeutic scope of conventional phage applications, ongoing research is exploring advanced delivery strategies – including encapsulation, cell-penetrating carriers, and phage-derived enzymes – to enhance intracellular targeting and extend phage-based interventions to such pathogens.

Role of Phage Therapy in Aquaculture and the One Health Paradigm

The integration of phage therapy into aquaculture represents a potentially sustainable approach to managing bacterial diseases in aquatic organisms and is conceptually well aligned with the One Health framework, which emphasizes the interconnectedness of human, animal, and environmental health (44). Within this paradigm, interventions aimed at improving animal health are also evaluated for their broader ecological and public health implications. The extensive use of antibiotics in aquaculture has been widely associated with the selection and environmental dissemination of AMR, raising concerns for both veterinary and human medicine. In this context, phage therapy offers a targeted alternative that may reduce selective pressure for antibiotic resistance and limit pharmaceutical residues in aquatic environments. While direct evidence linking phage use in aquaculture to measurable reductions in AMR transmission to humans remains limited, the preventive potential of phage-based interventions is increasingly recognized. By lowering bacterial disease burden in farmed fish and shellfish and reducing reliance on antibiotics, phage therapy may contribute to improved animal health, enhanced food security, and protection of aquatic ecosystems. Accordingly, bacteriophage-based interventions represent a vital component of the One Health framework for minimizing antibiotic reliance in aquaculture systems(45).

Future Perspectives and Research Priorities

The renewed interest in bacteriophage therapy underscores its potential role in addressing antibiotic resistance in aquaculture; however, translating experimental successes into reliable and scalable applications requires the resolution of several scientific and regulatory challenges. Future research should prioritize the standardization of experimental protocols, including consistent reporting of MOI, host species and size, water quality parameters, and baseline health status. Robust, placebo-controlled, and large-scale field trials are essential to validate phage efficacy under commercial farming conditions. In parallel, the development of phage formulations that are stable, scalable, and compatible with practical delivery routes such as feed incorporation, immersion, or injection is critical. Greater emphasis should also be placed on exploring phage-derived products, including endolysins, depolymerases, and engineered phage peptides, as alternative or complementary therapeutic agents. Finally, expanding host-range studies – particularly in underrepresented aquaculture species such as crustaceans and molluscs – will be necessary to broaden applicability. To facilitate regulatory approval and industry adoption, rigorous quality control standards and comprehensive genomic safety assessments must be systematically integrated throughout all stages of phage product development.

Conclusion

Aquaculture continues to be one of the fastest-growing sectors in global food production, yet its sustainability is frequently challenged by recurrent bacterial disease outbreaks. While antibiotics have traditionally played a central role in disease management, the alarming rise of MDR pathogens necessitates alternative strategies.

Bacteriophage therapy offers a promising, environmentally compatible, and cost-effective solution. It allows for precise targeting of bacterial pathogens with minimal disruption to host organisms and surrounding ecosystems. While challenges such as resistance, regulatory barriers, and standardization persist, the potential of phage therapy – particularly when combined with genomic tools, advanced delivery systems, and quality assurance practices – is significant.

Continued research, inter-disciplinary collaboration, and supportive policy frameworks will be crucial in advancing phage therapy from experimental concept to mainstream application in aquaculture disease management.

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