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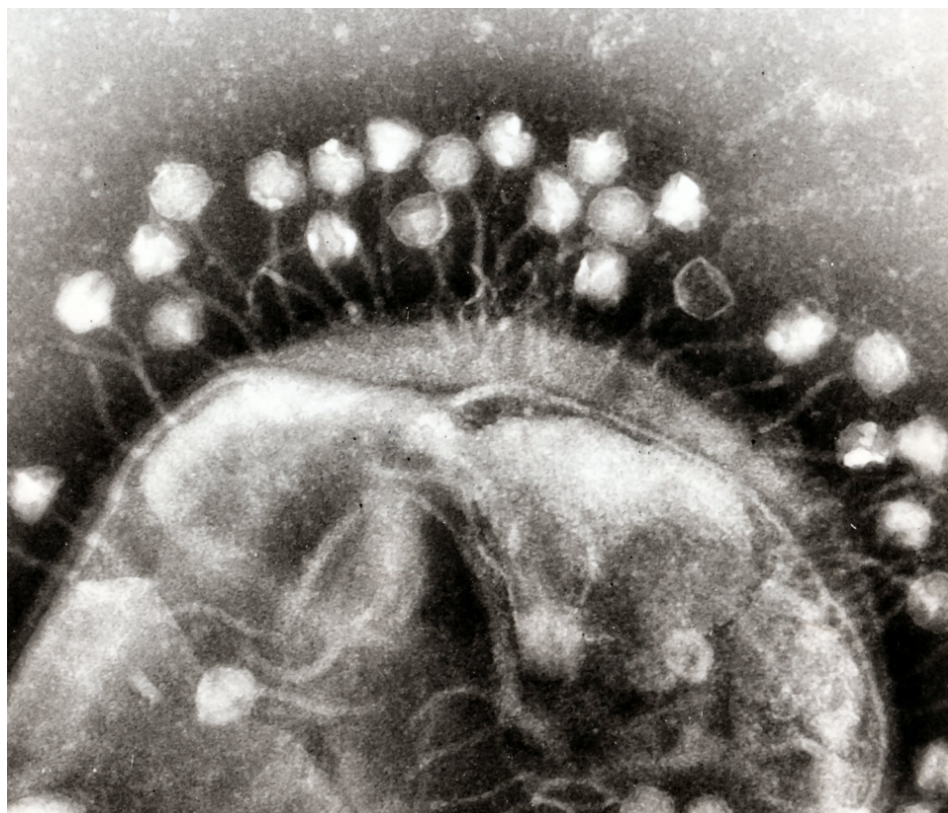
Health &
Welfare

A review of bacteriophage therapy in aquaculture

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Bacteriophage therapy needs more understanding of the susceptibility of virulent bacterial strains, their genetic traits involved in pathogenicity and phage-bacterium co-evolution



Study reviewed bacteriophage therapy in aquaculture, and reported that phage therapy as an alternative to antibiotics for treating bacterial diseases in aquaculture is still in the early stages of development but shows much potential; and that phage therapy needs more understanding of the susceptibility of virulent bacterial strains, their genetic traits involved in pathogenicity, and the phage–bacterium co-evolution. Photo by Professor Graham Beards (CC BY-SA 3.0, <https://creativecommons.org/licenses/by-sa/3.0>, via Wikimedia Commons) shows transmission electron micrograph of multiple bacteriophages attached to a bacterial cell wall; the magnification is approximately 200,000.

Bacteriophages are viruses that specifically target bacteria and, therefore, can be used to kill bacteria without harming animal cells. As such, they represent an attractive **alternative to antibiotics** (<https://doi.org/10.3390/antibiotics13040294>) in treating bacterial infections in both humans and animals. Bacteriophages vary greatly in size, morphology, genome, host specificity, and strain tropism. Depending on their replication strategy, bacteriophages are classified as lytic (virulent) or lysogenic (temperate). Lytic phages hijack bacterial cell machinery upon entry, rapidly replicate, and cause cell lysis, releasing hundreds of infectious viral particles ready to infect other host cells (productive infection). In contrast, lysogenic phages stably integrate their genome into the bacterial chromosome, persisting latently and replicating along with the bacterial chromosome.

Phage therapy offers advantages over antibiotics, such as self-replication (phages multiply in the presence of bacterial targets, allowing for smaller doses and lower costs), auto-dosing (phages disappear upon target bacteria elimination), lack of interference with non-target bacteria or body cells

(narrow action spectrum), and high strain specificity. However, the latter feature may be a disadvantage, which can be managed by using **bacteriophage cocktails** (<https://doi.org/10.2217/fmb.13.47>) (mixtures of different phages). Additionally, phages are more environmentally friendly than antibiotics, can clear biofilms too, and, due to their short development cycles, are low-cost and easy to use and store.

Phages co-evolve with their hosts, and counter-adaptation to developed resistance is likely to occur, ultimately benefiting bacteriophage therapy in the long term. To improve bacteriophage therapy, it is essential to expand the understanding of phages, particularly through the annotation of complete DNA genome sequences for accurate identification, prediction of transduction efficiency, and avoidance of undesirable elements. Additionally, it is also necessary to clarify the mechanisms behind the emergence of phage resistance, which are still largely unknown.

Bacteriophages were used against bacterial diseases in past centuries, during the pre-antibiotic era, although their nature was unclear. Western countries abandoned their use with the introduction of antibiotics, and it is only in recent years that they have been rediscovered and used in regulated clinical trials, well-documented in the scientific literature. This rediscovery was driven by the urgent need for alternative therapies due to the rise of clinically relevant multi-antibiotic resistance.



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This article – **summarized** (<https://creativecommons.org/licenses/by/4.0/c>) and adapted from the **original publication** (<https://doi.org/10.3390/microorganisms13040831>). (Albarella, D. et al. 2025. Bacteriophage Therapy in Freshwater and Saltwater Aquaculture Species. *Microorganisms* 2025, 13(4), 831) – discusses a review of the latest advancements in developing and applying bacteriophage therapy to treat the most common and economically impactful bacterial diseases in freshwater and saltwater aquaculture species.

Phage therapy in aquaculture

Bacterial diseases are the major challenge in aquaculture, resulting in huge economic losses. Aquatic animals are susceptible to numerous bacterial infections or co-infections, as they are exposed to a wide variety of pathogenic microorganisms in their environment.

In the absence of effective vaccines that could prevent the majority of diseases affecting aquatic species, or due to the practical impossibility of vaccinating fish at early life stages because of their small size or immature immune system, phage therapy plays the dual role of therapeutic and preventive measures against bacterial infections in aquaculture. This is especially important during larvae production, before the fish are introduced into aquaculture containers.

Phage therapy is crucial for reducing mortality due to bacterial infections in aquaculture. Successful application requires careful planning of the timing, dose, and frequency of phage delivery, considering the bacterial pathogen's virulence characteristics, the nature of the outbreak and the temporal dynamics of the major pathogenic bacteria. In this context, phage therapy is most effective during spring when

aquatic pathogenic bacteria exhibit the highest diversity, which correlates with a higher risk of outbreaks. Several factors influence the efficacy of phage therapy in aquaculture, including the fish's weight, the required phage dose, early disease diagnosis and environmental conditions.



Proteon Pharmaceuticals poised to grow its bacteriophage products for aquaculture

Bacteriophage producer nets €21 million to accelerate the commercialization of its products, which aim to reduce antibiotic usage in aquaculture.



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The selection of the phage delivery route depends on the nature of the infection, the size of the farm, the cost of phage preparation, and the fish species. The three primary methods for administering phages in aquaculture are immersion, injection, and oral administration. Immersion is less time-consuming, while injections, which are ideal for systemic infections, are more time-consuming and invasive, potentially causing high mortality. Oral administration is considered the most practical method due to its low cost and minimal stress on the fish.

However, challenges include the loss of phage stability and the acidic, proteolytic conditions in the gut, which may require coating systems or the addition of acid neutralizers to the phage suspension. Bacteriophages should be able to endure dry conditions on feed following coating for oral feed applications. Longer phage survival is critical for reducing feed preparation costs and maximizing commercial benefits.

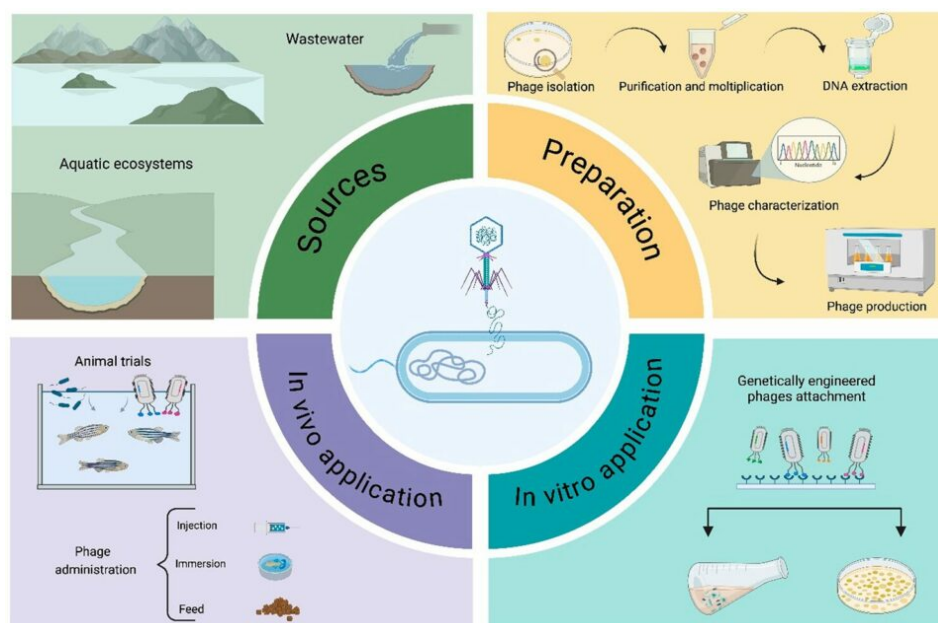


Fig. 1: Bacteriophage therapy in aquaculture. Phages are collected from natural and wastewater sources, isolated and characterized in the laboratory, and engineered before being tested *in vitro*. The selected modified phages are then tested *in vivo* on infected animals.

Phage therapy in fish culture

Aquaculture wastewater and the environment have both been found to contain **numerous antibiotic-resistant genes and antibiotic-resistant bacteria** (<https://doi.org/10.1016/j.watres.2020.116455>). As a result, bacteriophages may be employed as alternatives to antibiotics, helping to reduce antibiotic usage at the source and address concerns related to antibiotics. However, currently, phages are primarily used in research at the bench level or in small-scale trials to prevent and control antibiotic-resistant bacterial infections in aquaculture. Research on the interactions between phages and their aquatic hosts has mainly been conducted in marine environments, with relatively little focus on freshwater ecosystems.

Phage research has focused on some bacterial species belonging to the genera *Aeromonas*, *Vibrio*, *Edwardsiella*, *Streptococcus*, and *Flavovacterium*, which are particularly pathogenic for fish, mollusks and crustaceans. Less information is available on other genera, although these pathogens can still cause significant economic damage to the aquaculture industry. *Aeromonas* spp. is the pathogen for which the highest number of *in vivo* trials have been performed, followed by *Vibrio* spp., particularly in larvae models.

Edwardsiella spp. are important pathogenic bacteria affecting several species of commercially cultured fishes, mollusks and crustaceans.

Photo of *Edwardsiella anguillarum* by Leibniz-Institut DSMZ (CC BY 4.0, <https://creativecommons.org/licenses/by/4.0>, via Wikimedia Commons).

Phage therapy in mollusk culture

Bacteriophage therapy may also be effective in treating bacterial infections in mollusk species, with the most targeted bacteria being *Vibrio* spp., followed by *Escherichia coli* and *Salmonella enterica*. The most commonly affected animals are oysters and abalones.

The spread of *Vibrio* spp. in marine, estuarine, and freshwater environments is responsible for vibriosis, a devastating disease that can cause up to 100 percent mortality in contaminated facilities, not only in fish but also in shellfish. These shellfish can pass the pathogen to humans through the consumption of raw or improperly cooked seafood.

Among the numerous infectious *Vibrio* species, *V. parahaemolyticus* is considered one of the primary foodborne pathogens worldwide, while *V. coralliilyticus* and *V. tubiashii* are responsible for high mortality rates in oysters, leading to significant economic losses globally. The approach to managing these species varies depending on the goal: for *V. parahaemolyticus*, research primarily focuses on using phages to purify oysters and ensure their safety for human consumption. In contrast, for *V. coralliilyticus* and *V. tubiashii*, phage therapy is aimed at safeguarding the health of oysters and other mollusk species.

Apart from the public health impact, an outbreak of *V. parahaemolyticus* has significant social repercussions for the entire shellfish-producing region. Additionally, *V. parahaemolyticus* strains infecting seafood have shown resistance to multiple commercial antibiotics, similar to strains infecting

humans, and as a result, the potential of various candidates for bacteriophage therapy has been investigated both *in vitro* and *in vivo*.

Phage therapy in crustacean culture

Vibrio parahaemolyticus is one of the most prevalent foodborne pathogens worldwide, and also responsible for significant mortalities in several farmed mollusk and crustacean species. Photo by Janice Carr
Content Providers(s): CDC/ Janice Carr (Public domain, via Wikimedia Commons).

Among bacteria, *Vibrio* spp. is the leading cause of economic losses in the shrimp industry, followed by *Aeromonas* spp. All stages of the shrimp life cycle, from eggs to broodstock, can be affected by *Vibrio* spp. infection, which typically results in 100 percent mortality in contaminated facilities. The genus *Vibrio* includes a range of pathogenic species that impacts not only the farming of fish and mollusks but also the farming of crustaceans. Therefore, alternatives to disinfectants and the limited number of allowed antibiotics are being explored, with bacteriophage therapy emerging as a promising option. Some phages target multiple *Vibrio* spp., while others are specific to certain highly pathogenic strains. Among the *Vibrio* species, the most pathogenic in crustaceans are *V. parahaemolyticus*, *V. harveyi*, and *V. alginolyticus*.

V. parahaemolyticus is regularly monitored in shrimp hatcheries, not only because it is the primary cause of seafood-related bacterial gastroenteritis globally, but also because it causes necrosis, stunted growth, muscle opacity, anorexia, and, ultimately, death in crustaceans. Some strains are responsible for Acute Hepatopancreatic Necrosis Disease, characterized by mortality rates of up to 100 percent in marine shrimp aquaculture.

Since the proportion of a particular microorganism impacts others and the entire microbial community, and given that the gut microbiota of shrimp influences their health, phage therapy may serve as an effective measure to prevent acute hepatopancreatic necrosis disease in the shrimp industry. Furthermore, since acute hepatopancreatic necrosis disease may be caused by various pathogenic strains of *V. parahaemolyticus*, developing bacteriophage cocktails effective against a broad range of *V. parahaemolyticus* strains is particularly beneficial.

Several studies have researched the use of various bacteriophages to manage pathogenic *Vibrios* (refer to the original publication). These include *V. campbellii*, is emerging as an opportunistic pathogen associated with luminous vibriosis and potentially linked to acute hepatopancreatic necrosis disease. *V. harveyi* is a prevalent cause of mortality in hatcheries and culture systems for larval shrimp, in addition to being a pathogen for fish, as mentioned above. *V. alginolyticus* is another significant pathogenic species that infects a variety of aquatic organisms, including crustaceans, mollusks, fish and humans, where it causes skin and ear infections, as well as acute gastroenteritis.

Various *Vibrio spp.* cause significant mortalities in penaeid shrimp hatcheries worldwide. Photo of black tiger shrimp (*Penaeus monodon*) postlarvae in rearing tank at commercial hatchery by Darryl Jory.

Perspectives

Phage therapy is increasingly considered the most promising alternative to treat bacterial diseases in cultured aquatic organisms. Aquaculture's bacteriophage therapy has only gained popularity in recent years, and as a result, the number of studies available is fewer compared to other livestock sectors. The conditions to consider when applying phage therapy in aquaculture are varied and depend on the type of farming. For example, crustaceans have very different requirements compared to fish. Therefore, the stability of phages under certain conditions, such as water salinity, temperature, pH and ultraviolet radiation, is much more stringent.

Most bacteriophages studied have been tested *in vivo*; however, for those tested only *in vitro*, it remains impossible to directly translate the results obtained *in vitro* to an *in vivo* system. Another issue is that most of the phages used in aquaculture have not been fully characterized in terms of their genomic and proteomic features, so there is limited information on their full potential and possible toxicity to the organism. Indeed, the major limitation to the application of bacteriophage therapy in aquaculture is the lack of comprehensive data, which in turn restricts the genetic engineering of the phages themselves.

Another challenge is the rise of phage-resistant, mutated pathogenic bacterial strains. In this context, cocktails of multiple bacteriophages are the preferred option for combatting multidrug-resistant pathogens. As demonstrated by several comparative studies between single phages and phage cocktails, the latter has proven to be more efficacious in the vast majority of cases. Additionally, the delivery method also impacts on the efficacy of phage therapy.

Administration varies depending on the characteristics of the phage, the nature of the infection, and the animal species. In aquaculture, injection is generally the most effective method for targeting bacteria that cause clinical signs in internal organs, but this method is associated with a high mortality rate. Moreover, when animals are small and numerous, injecting phages can be labor-intensive and time-consuming. Therefore, phage-incorporated diets (phage-coated feeds) have been successfully used to treat large quantities of fish, ensuring continuous delivery of phages at designated times.

Overall, phage therapy as an alternative to antibiotics for treating bacterial diseases in aquaculture is still in the early stages of development. It requires further understanding of the phage susceptibility of virulent bacterial strains, their genetic traits involved in pathogenicity, and the phage–bacterium co-evolution before it can be fully validated.

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