A War Beneath the Water: Bacteria, Bacteriophages and the Future of Aquaculture Disease Management

Chandru Govindan[1] and Arun Sharma[1]*

[1]*Department of Aquatic Animal Health Management, ICAR-Central Institute of Fisheries Education, Off Yari Road, Versova, Andheri West, Mumbai- 400061, Maharashtra, India.*

Corresponding Author
Arun Sharma
Email: arunsharma@cife.edu.in

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ABSTRACT

Bacterial diseases, which affect the health, production efficiency, and economic sustainability of aquaculture, are becoming an increasing problem. Meanwhile, the widespread use and misuse of antimicrobial agents have also been responsible for the spread and emergence of antimicrobial-resistant bacteria, highlighting the need to find safer and more effective ways to manage diseases. Bacteriophages are viruses that target bacterial cells and are being studied more and more for biological approaches. There are many anti-phage defence mechanisms in bacteria, which can prevent phage adsorption, inhibit genome injection, degrade phage nucleic acids, and end infected cells before productive phage replication. In response, bacteriophages are constantly developing defenses such as production of depolymerase, nucleic acid modification and anti-CRISPR mechanisms, as well as diversification of receptors to which they bind. Bacteriophages, in turn, are constantly evolving defenses, such as the ability to produce depolymerases, to modify nucleic acids, and to provide anti-CRISPR mechanisms, while they are evolving the ability to bind to different receptors. This co-evolution is an ‘arms race' that affects the dynamics of bacterial populations, the diversity of phages, and the success of phage therapy interventions. This article discusses the phases of the evolutionary arms race between bacteria and phages, their application to aquaculture disease management, and the potential of phages for sustainable management of aquatic animal diseases.

INTRODUCTION:

Every aquaculture system has an intricate microbial community that interacts with bacteria and their predators (viruses) constantly and continuously. One of the most dynamic examples of microbial co-evolution is that of bacterial pathogens and bacteriophages. Phages, or bacteriophages, are viruses that specifically target bacterial cells. Bacteriophages are estimated to be present at approximately 10 times the abundance of bacteria in the world, an estimated 10^{31} particles, which suggests that they are important in the regulation of bacterial abundance in various ecosystems and environments (Breitbart and Rohwer, 2005).

The interaction between a bacterium and a phage has been simplified and reduced to infection and subsequent bacterial lysis. Actually, the result depends upon a series of molecular interactions. To infect the bacteria, the phage has to recognize a suitable receptor, bind to the cell surface, and inject its genetic material. The bacterial cell, on the other hand, has several ways of disrupting each of these phases. The probability of productive phage infection can be diminished by surface receptor modification, extracellular barriers, restriction-modification systems, CRISPR-Cas immunity, abortive infection, and several other recently discovered defence systems.

This ancient evolutionary process has acquired new importance in aquaculture. These are the important genus of bacterial pathogens *Aeromonas, Vibrio, Flavobacterium, Edwardsiella,* and *Pseudomonas,* which have been correlated with significant diseases of cultured fishes. Furthermore, the global use of antimicrobials in fish culture will increase by approximately 33% until 2030, highlighting the need for alternative solutions to disease management in fish culture (Schar *et al*., 2020). Phage therapy is thus a possible alternative approach to conventional antimicrobial therapy. Previous studies have reported that phages are effective in controlling some bacterial diseases in fish and shellfish, and the efficacy relies on the characteristics of the phage, bacterial susceptibility, dosage, administration, and environmental conditions.

Understanding these mechanisms helps in designing engineered phages to overcome bacterial defense mechanisms and enhance therapeutic effects (Oechslin, 2018). This constant state of defence and counter-defence is an evolutionary arms race, and it has significant implications for sustainable aquaculture.

First Strike: The Phage Infection Cycle

The process of infection starts with the bacteriophage specifically attaching to the bacterial cell surface, and the phage genes are injected into the cell. The intracellular phage genome can then take three different courses: lytic, lysogenic, or pseudolysogenic. In the lytic cycle, the phage replicates and directs the synthesis of structural proteins, making progeny virions, and ultimately the host cell lyses. The lysogenic cycle involves the stable integration (prophage) of the phage genome into the bacterial chromosome with its subsequent replication with the host genome. Pseudolysogeny refers to the situation in which the phage genome survives inside the cell but is not integrated into the chromosome and does not replicate immediately, usually under nutrient-limiting or physiological stress conditions. In this sense, strictly lytic phages are preferred in phage therapy as they only have bactericidal activity without lysogeny.

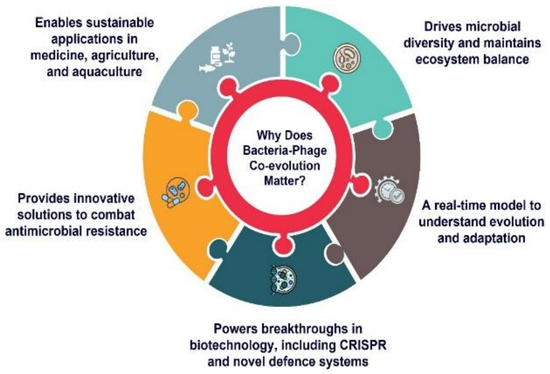

Figure 1: Significance of Bacteria-Phage Co-evolution

Bacterial Anti-Phage Defence and Phage Counter-Adaptation

1. **Receptor Modification and Receptor-Binding Adaptation:** Bacteria can modify, mask, or lose surface receptors required for phage adsorption. To overcome this, phages might evolve modifications in tail fibers, tail spikes, and receptor-binding proteins that enable them to recognize new receptors.

2. **Capsule and Biofilm Formation and Depolymerase-Mediated Penetration:** Bacterial capsules and biofilm-associated extracellular polymeric substances may limit the ability of phages to access the bacteria. To overcome these barriers, some phages produce polysaccharide depolymerases that break down the components of the bacterial capsule or biofilm, allowing the phages to infect the bacteria.

3. **Superinfection Exclusion and Infection-Evasion Strategies:** Superinfection exclusion is the ability of an infected cell to block the entrance or establishment of productive infection of secondary phages. The phages can circumvent these barriers by changing adsorption, the process by which their genomes are delivered into the host, or the processes by which they infect the host's cells, but the particular counter-mechanism is very specific to the phage-host system.

4. **Restriction-Modification Systems and Phage Genome Protection:** Bacterial restriction enzymes recognize and cleave invading phage DNA. To overcome this defense, phages modify their DNA, alter restriction-sensitive sequences, and also produce anti-restriction proteins to decrease the degradation of their genomes.

5. **CRISPR-Cas Immunity and Anti-CRISPR Mechanisms:** CRISPR-Cas systems detect and attack the sequences of phages from past infections. Phages have developed genome-protection mechanisms and mutations to the target sequences, as well as anti-CRISPR proteins, to avoid CRISPR interference.

6. **Abortive Infection and Phage Escape Mechanisms:** In abortive infection, the bacteria grow but are not productively infected. Phages can overcome certain Abi systems by mutating their genes or by expressing a factor that blocks the bacterial defence pathway.

Impact of phage resistance	Consequence in aquaculture
Treatment failure	Phage-sensitive bacteria are killed, but resistant variants survive and continue multiplying, potentially causing disease recurrence.
Reduced efficacy of single-phage therapy	A single phage generally has a narrow host range, so resistant or naturally non-susceptible pathogen strains may remain untreated.
Persistence of pathogenic bacteria	Resistant bacteria can survive phage exposure and maintain the pathogen population in culture water, biofilms, or fish.
Disease recurrence	Surviving resistant bacteria can multiply after phage titres decline, potentially resulting in renewed

Impact of phage resistance	Consequence in aquaculture
	infection and mortality.
Complicated disease management	Continuous monitoring of pathogen susceptibility may become necessary, increasing the complexity of phage-based disease management.
Selection for altered bacterial phenotypes	Mutations that prevent phage adsorption may alter bacterial surface structures and potentially affect bacterial fitness or other phenotypes.
Greater risk in intensive production systems	High pathogen density and repeated phage exposure can create strong selection pressure for resistant bacterial populations.

Table 1: Phage Resistance and its impact on Aquaculture

Humans as a Third Player in the Bacteria-Phage Arms Race

1. **Antibiotic Resistance Changes the Battlefield:** The application of antibiotics, disinfectants, and phage therapy generates new selection pressures, which further speed up the adaptation process of bacteria and phages. Multidrug-resistant bacteria are selected through the inappropriate use of antibiotics and can become susceptible to new phages and acquire new defence strategies. This can make control of diseases using phages more difficult.

2. **Phage Therapy: A New Evolutionary Pressure:** When humans introduce therapeutic phages, bacteria are forced to evolve new defence mechanisms. Concurrently, phages can evolve as well to conquer bacteria, thus giving rise to another artificial stage of the evolutionary arms race.

3. **Pollution Connects Different Microbial Worlds:** Antibiotics and resistant bacteria, resistance genes and phages may enter the same place in the environment through agricultural runoff, domestic sewage and aquaculture effluents. This makes it possible for genetic exchange and alters the evolutionary landscape of microbial communities.

4. **Climate Change:** Increasing temperatures and fluctuations in environmental conditions may affect the growth of bacteria, the dynamics of disease outbreaks, and the interaction between phage and host, thereby potentially altering the rate and direction of co-evolution in aquaculture systems.

5. **Engineering the Arms Race:** The application of synthetic biology and genome editing enables researchers to precisely engineer phages for greater specificity towards bacterial pathogens. Although this can offer an alternative to antibiotics, engineered phages must be treated with caution due to their ecological and evolutionary implications.

Mitigation Strategies for Phage Resistance

- **Phage Cocktails:** Phage cocktails are comprised of mixtures of different phages targeting different bacterial receptors to reduce the risk of resistance developing and increase the efficacy of treatment.

- **Phage-Antibiotic Synergy:** The combination of the appropriate antibiotic with the appropriate phage is an effective way of increasing the effectiveness of killing bacteria and preventing the emergence of phage-resistant mutants.

- **Engineered Phages:** We can modify the phages to have broader host ranges, improved infectivity, or the ability to produce enzymes that degrade biofilms, or even have ways to overcome the bacteria's CRISPR defenses.

- **Phage Rotation:** Rotating the use of different phages in sequence can help minimize the continuous selection pressure and slow the emergence of resistance.

- **High-Throughput Phage Screening:** Screening of phage libraries against a specific pathogen quickly will yield effective phages as soon as resistance begins to emerge.
- **Ecological Monitoring:** Regular assessment of phages, bacteria, and other non-target microbial communities is essential to ensure the efficacy of the treatment and preservation of beneficial microbiota.
- **Combination of Multiple Strategies:** A sustainable approach to combat phage resistance in aquaculture may be a combination of multiple strategies, such as phage cocktails, antibiotics, engineered phages, phage adaptation, and biofilm disruption.

CONCLUSION

The never-ending war between bacteria and phages is a mighty engine of evolution, not just a war of microbes. Understanding these molecular interactions provides the foundation for the development of sustainable, precision-based strategies for the control of bacterial diseases and the fight against antimicrobial resistance. Engineered phages, phage cocktails, and phage-antibiotic combinations are adaptive strategies that will improve the long-term efficacy and durability of phage therapy. The use of phage-based interventions in a One Health approach will decrease reliance on antibiotics and foster sustainable disease management in aquaculture, agriculture, veterinary and human medicine.

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