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Review

Bacteriophages in the Control of *Aeromonas* sp. in Aquaculture Systems: An Integrative View

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Abstract: *Aeromonas* species often cause disease in farmed fish and are responsible for causing significant economic losses worldwide. Although vaccination is the ideal method to prevent infectious diseases, there are still very few vaccines commercially available in the aquaculture field. Currently, aquaculture production relies heavily on antibiotics, contributing to the global issue of the emergence of antimicrobial-resistant bacteria and resistance genes. Therefore, it is essential to develop effective alternatives to antibiotics to reduce their use in aquaculture systems. Bacteriophage (or phage) therapy is a promising approach to control pathogenic bacteria in farmed fish that requires a heavy understanding of certain factors such as the selection of phages, the multiplicity of infection that produces the best bacterial inactivation, bacterial resistance, safety, the host's immune response, administration route, phage stability and influence. This review focuses on the need to advance phage therapy research in aquaculture, its efficiency as an antimicrobial strategy and the critical aspects to successfully apply this therapy to control *Aeromonas* infection in fish.

Keywords: phage therapy; *Aeromonas* species; bacterial infections; aquaculture; fish

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1. Introduction

Increasing global production to offset progressive worldwide reductions in the amount and quality of natural seafood populations has contributed to making aquaculture one of the fastest-growing productive agricultural sectors. In the last few years, aquaculture rapidly expanded its driving economic growth and contributed to global food security [1]. In 2018, almost 38% of all fish caught or farmed worldwide were traded on international markets, generating a total value of 164 billion USD [1]. However, aquaculture industries often suffer extensive financial losses due to uncontrolled microbial diseases, threatening their sustainability and growth [2]. The main biological agents responsible for waterborne diseases include bacteria, viruses, protists, helminths, fungi and oomycetes [2–4]. However, bacteria are the main cause of infections and the major concern in the aquaculture industry, leading to large financial losses that endanger the sector's sustainability and causing heavy losses to fish farming plants [2–5]. The main bacterial diseases in aquaculture are vibrosis, aeromonasis, edwardsiellosis, pseudomonasis, flavobacteriosis, mycobacteriosis, streptococcosis, renibacteriosis, infection with anaerobic bacteria (*Clostridium botulinum* and *Enterobacterium catenabacterium*) and intracellular bacterial infection (*Francisella noatunensis*, *Piscirickettsia salmonis*, *Hepatobacter penaei*, *Chlamydia* spp.) [6–8]. Aeromonasis in fish is caused by *Aeromonas* species, namely *A. hydrophila*, *A. salmonicida*, *A. caviae*, *A. sobria*, *A. veronii* and *A. jandaei* [9–11]. These species are common in freshwater habitats and are frequently associated with severe infections and mortality in various freshwater and marine fish [12–15].

Disease prevention in aquaculture species includes several strategies and management solutions, including vaccines and antibiotics. Vaccination is considered crucial as it is one

of the main approaches to prevent and control diseases in aquaculture [16]. Currently, there are over 26 vaccines approved for a variety of fish species [6,17–20]. This set of vaccines has proven to successfully protect fish against a variety of severe diseases [20]. Most vaccines are based on inactivated microorganisms and adjuvants delivered through immersion or injection [20]. Live vaccines are more efficient because they generate a strong antibody response by mimicking the natural pathogen infection and have a greater potential to be administered via oral or by immersion [20]. Prophylactic immunization for bacterial diseases in farmed fish has been attempted with some success against *Yersinia ruckeri* and *A. salmonicida* [21]. Despite some successes, there are no vaccines available for many of the pathogens [2,22–24]. Moreover, the vaccines that exist, do not always offer thorough protection nor can they be used to protect juvenile fish, which lack a mature immune system [24]. In addition, the development of new fish vaccines can be expensive and vaccination is impractical in small animals such as the fish larvae, which are usually more susceptible to disease, and cannot develop specific immunity [2,22–24].

To overcome these constraints, aquacultures have resorted to antimicrobial drugs to treat bacterial fish diseases or as a preventive measure administered in feeds [25]. This results in environmental leakage of these chemicals and selection of resistance. The prolonged presence of antibiotics, even at concentrations lower than the minimum inhibitory concentration, in the polybacterial matrices of ponds, sediments, or biofilms can provoke a selective pressure on the bacterial populations and the consequential exchange of antimicrobial genes between bacteria [25–28]. The transition of antimicrobial residues, antimicrobial-resistant bacteria and resistance genes from the aquatic environment to terrestrial livestock and humans presents an increased risk of wide-spreading drug resistance [29]. The emergence of antibiotic-resistant *Aeromonas* strains in aquaculture has been observed [30,31], making it urgent to find alternative control methods to treat these infections. Phage therapy appears as an efficient, environmentally friendly and empirical solution to control pathogenic bacteria in farmed fish.

Phages are bacteria-infecting viruses that are abundantly present in the environment and essential in controlling bacterial populations in natural systems [2,32]. Their potential use in agriculture, aquaculture, veterinary, food safety and medicine is being studied worldwide [2,33–49]. In recent years, the use of phages to inactivate pathogenic bacteria in farmed fish has gained momentum, mainly due to their inherent low toxicity [32]. This growing trend seems to show an increased interest in industrial applications of phages in aquaculture. However, only one phage-based product, called BAFADOR®, was approved for use to control *Pseudomonas* and *Aeromonas* in aquaculture [50].

This review highlights and discusses the potential that phage therapy has to control *Aeromonas* in fish, the main preventive measures used and the aspects that need to be considered when applying phage therapy in aquaculture.

2. *Aeromonas* Infections

The fish farming industry is heavily affected by pathogenic bacteria infections that can become one of the main sources of financial loss [2,51,52]. Unfavorable conditions found in fish farms, such as high fish density, high temperatures, rapid growth, overfeeding and residue accumulation, increase the possibility of pathogen transmission between individuals and can consequently provoke disease outbreaks. Furthermore, when sick or dead fish are not extracted from the farming area in time, the risk of disease increases, allowing pathogens to become more aggressive in the already polluted environments. It has been shown that pathogenic microorganisms are introduced by wild fish into the aquatic environment and not farmed fish, as was previously thought [2].

The genus *Aeromonas* (phylum, Proteobacteria; class, γ-Proteobacteria; order, Aeromonadales; and family, *Aeromonadaceae*) comprises a group of Gram-negative bacteria, widely distributed in aquatic environments, being easily isolated from animals such as fish and crustaceans [53–55], and comprises a total of 36 species that are currently described in the genus [53]. The members of the genus *Aeromonas* can be split into two groups based

on their biochemical characteristics and growth conditions: psychrophilic, composed of non-motile bacteria with optimal growth between 22–25 °C; and mesophilic, composed of mobile bacteria with a single polar flagellum in most of the species and an optimal growth at 35–37 °C [53–55]. Table 1 summarizes the general characteristics of the genus *Aeromonas* members. The ability to adapt enables *Aeromonas* to colonize terrestrial environments and their inhabitants, allowing them to be found in sources, such as soils, plants, fruits, vegetables, birds, reptiles, amphibians, among others [54]. Some species can cause disease in humans, fish and other aquatic animals. Infectious processes usually develop in immunocompromised hosts; however, in fish and other marine animals, virulent strains have already been reported [11,56,57]. Although the way how these pathogens are transmitted is still unclear, species such as *Aeromonas* (e.g., *A. hydrophila*, *A. caviae*, and *Aeromonas dhakensis*) are well known as causative agents of human diseases, including gastroenteritis, soft tissue infections, septicemia, peritonitis, pneumonia and diarrhea [58,59]. *A. caviae*, *A. hydrophila, A. sobria*, *A. salmonicida*, *A. jandaei*, *Aeromonas bestiarum* and *A. veronii* are typically associated with fish diseases and mortality [9–11]. Supplementary Materials Table S1 lists the common *Aeromonas* sp. that are detected in fish. Motile *Aeromonas*, such as pathogenic bacteria, can be responsible for fish deaths up to 80–100% within 1–2 weeks, leading to substantial economic losses in commercial carp farming due to high mortality rates and producing quality degradation [60–62]. The main species affected by disease and death caused by these pathogens are carp, tilapia, rainbow trout, brown trout, eel, perch, catfish, goldfish and salmon [63]. *Aeromonas* virulence is complex because several factors significantly contribute to the development of the infectious process as the effectiveness of the host immune system decreases [5,64]. Structural components, toxins and extracellular products, acting jointly or individually, enable these microorganisms to colonize and infect hosts [9,54,65,66]. Virulence factors can be expressed differentially between species, making some strains more virulent than others [54]. Some of the most relevant fish diseases that result in major die-offs and fish kills and are caused by the above factors are: external ulcerative lesions, fin and tail rot, red sores, ocular ulceration, anal region pale body colour, reddish head, fin haemorrhagic, septicaemia, hemodiapedesis, anorexia, exophthalmos and erythrodermatitis, revealed clear ascites, haemorrhages and destruction of sheathed tissues in spleen and renal tubular necrosis in the kidney, liver congestion, enlargement of spleen and kidney and enteritis [67–69]. *Aeromonas* infection signs and symptoms may vary depending on the location of the infection and the type of bacteria (Table S1).

A. salmonicida and *A. hydrophila*, the most studied species in aquaculture within the *Aeromonas* genus, are relevant fish pathogens in aquaculture, responsible for significant economic losses worldwide due to high mortality and morbidity in several fish species.

A. salmonicida is one of the main pathogens responsible for furunculosis in wild and cultured salmonids, causing bacterial septicemia in fish [55,70], and can infect several fish species such as Arctic charr (*Salvelinus alpinus*), Atlantic cod (*Gadus morhua*), Atlantic halibut (*Hippoglossus hippoglossus*), Atlantic salmon (*Salmo salar*), Atlantic wolffish (*Anarhichas lupus),* carp (*Cyprinus carpio*), Chinese perch (*Siniperca chuatsi*), flounder (*Platichthys flesus*), goldfish (*Carassius auratus*), lumpsucker (*Cyclopterus lumpus*), rainbow trout (*Oncorhynchus mykiss*), spotted wolfish (*Anarhichas minor*) and turbot (*Scophthalmus maximus*) [70–73]. Although *A. salmonicida* is only regarded as a primary pathogen in fish and not in humans because of its inability to grow at 37 °C, several studies have demonstrated its ability to cause human infections that result in septicemia and endocarditis [74–76].

Table 1. List of some general characteristics of members of the genera *Aeromonas*.

Characteristic	Description	References
Habitat	Distributed in aquatic environments, usually isolated freshly from different water sources (sea, reservoirs and sewage). Some species can be isolated from healthy and diseased fish, chironomid egg masses and intestinal/extraintestinal human samples.	[53,77]
General morphological characteristics	Gram-negative bacilli	[53,77]
General biochemical characteristics	Some species have mobility (e.g., *A. hydrophila*, *A. caviae* and *A. veronii*) Facultative anaerobes; Oxidase positive; Catalase positive; Capable of degrading nitrates to nitrites, glucose fermenters; Resistant to vibriostatic agent O/129 (2,4-diamino-6,7 diisopropylpteridine) at concentrations of 150 mg/disc with few exceptions (*Aeromonas australiensis* and *Aeromonas cavernicola* and a few *Aeromonas eucrenophila* and *A. veronii* strains).	[53,77]
Isolation and cultivation media	General: Tryptic soy agar (TSA) and Tryptic Soy Broth (TSB). Specific: Starch-ampicillin agar; Taurocholate-tellurite-gelatin agar; Ampicillin dextrin agar; Cefsulodin-irgasan-novobiocin agar, MacConkey agar and blood agar enriched with ampicillin; Glutamate starch phenol red and Aerosmart AH medium.	[54,58,78–82]
NaCl tolerance	*Aeromonas* can tolerate up to 5% NaCl for growth.	[83,84]
Optimum growth temperature	*Aeromonas* grow best at temperatures between 22 °C and 37 °C, depending on the strain under analysis. Psychrophilic *Aeromonas* (e.g., *A. salmonicida*), grow at temperatures lower than 22–25 °C. Mesophilic *Aeromonas* (e.g., *A. caviae*, *A. hydrophila*, *A. veronii*), grow at temperatures between 35–37 °C. Survive in low temperatures (2–10 °C).	[83]
Optimum growth pH	Survive at pH = 5	[84]
Virulence factors and pathogenicity	Structural components (e.g., flagella, pili, proteins and membrane antigens). Extracellular products: (e.g., hemolysin, protease, lipase, protease, DNases cytotoxic enterotoxin) Secretion systems: Type II secretion system Type III secretion system Type IV secretion system Type VI secretion system	[54,85,86]

A. hydrophila is an opportunistic pathogen with a wide host range (e.g., amphibians, birds, fish, reptiles and mammals) [87,88] and is responsible for several bacterial diseases that have caused the loss of millions of dollars in the global freshwater aquaculture industry [6,63,89]. *A. hydrophila* can infect several freshwater and marine fish, causing "Motile *Aeromonas* Septicemia (MAS)", or "Red-Sore Disease" [90], which results in lesions, scale shedding, gill and anal hemorrhage, abdominal swelling, skin ulcers and septicemia [91]. Different fish species, including tilapia (*Oreochromis niloticus*), catfish (*Ictalurus punctatus*), striped catfish (*Pangasianodon hypophthalmus*), goldfish (*C. auratus),* common carp (*C. carpio*) and eel (*Anguilla* spp.) are affected by *A. hydrophila*. The high mortality, weight loss and high treatment costs lead to severe economic losses to the aquaculture industry [6,92–96].

3. Disease Control and Alternative Approaches

Sustainably preventing aquaculture diseases is desirable, but not always possible since supplying the optimal conditions and feeding can be economically challenging. Furthermore, its success may require effective biocontrol techniques to reduce infections [97,98]. The rapid spread and the ubiquitous nature of fish pathogenic microorganisms mean that infection control and prevention can be difficult [99,100]. Preventing and controlling dis-

eases in aquaculture becomes more challenging with: (1) severe fecal contamination in fish farm waters [101,102], because few medications are licensed for use in fisheries [2,25] and many chemotherapeutic agents are ineffective against endospores and zoospores, leading to treatment failure in the case of infection [103,104]; (2) irregular environmental conditions (e.g., elevated temperatures, salinity variations, decreased oxygen concentrations, high organic load) that may contribute to disease outbreaks, often weakened by the sensitive fish's innate defense system [98,102,105]; (3) high fish densities (greater than the indicated for each species), common practice in farming systems, which reduces infection resistance [106]; (4) different stages of the fish life cycle, that affect the development of the immune system, increases the frequency of infections [106,107]; (5) the indiscriminate and prophylactic use of antibiotics that increases the resistance problem in common pathogenic bacteria and the concern with the antibiotic spread in the environment [25,28,108].

Despite the growing concern about the emergence of antimicrobial resistance in bacteria, pathogen control in aquaculture is still mostly reliant on antibiotic usage [55]. It is difficult to know exactly how much antibiotics are used in aquaculture [109] since it depends on the antibiotics, the authorized limits in each country, the various farming types and the diversity of aquaculture species [110–113]. A drastic reduction in antibiotic use has been seen in recent years in some countries due to vaccination and improved husbandry practices [112–115], particularly in Norway [116]. However, antibiotics were and are abusively applied in some countries, such as China, Vietnam and India, to promote growth, as well as to treat and prevent diseases [39,117,118]. According to Lulijwa et al. (2020), 73% of the main aquaculture producing countries use florfenicol, sulphadiazine and oxytetracycline and 55% applied amoxicillin, erythromycin, enrofloxacin and sulfadimethoxine [108]. The United States (USA), the European Union (EU) and Japan, have strict regulations on the use of antibiotics and restrict minimum limits approved in aquaculture. [25]. In 2006, the EU banned the use of antibiotics as growth promoters in farm animals [119]. The U.S. Food and Drug Administration (FDA) only allows the use of florfenicol, oxytetracycline and sulfadimethoxine/ormetoprim in the aquaculture industry [25,113]. The United Kingdom (UK) only allows amoxicillin, cotrimazine, oxolinic acid, oxytetracycline and sarafloxacin [25,113]. China and Vietnam, on the other hand, are the main consumers of antibiotics, which might explain their rampant prophylactic use [108]. The Chinese government currently allows the use of 13 antibiotics (doxycycline, enrofloxacin, florfenicol, flumequine, neomycin, norfloxacin, oxolinic acid, sulfamethazine, sulfamonomethoxine, thiamphenicol and trimethoprim) [108,110]. Until 2014, 30 antibiotics were authorized in Vietnam. But even though they also banned ciprofloxacin and fluoroquinolones in 2016, their presence is still detected in later studies. While Vietnam and China have relatively big domestic markets, the other Asian countries, such as India, Thailand, South Korea and Bangladesh, have to use fewer antibiotics to meet the strict regulations of their trading partners, namely the USA, the EU and Japan [108,120,121]. The antibiotics used in aquaculture production by the 15 major producers (2008 to 2018) have been described by Lulijwa et al. (2020) [108].

The regular and massive use of antibiotic prophylaxis in aquaculture systems has resulted in the emergence of multidrug-resistant bacteria, including *Aeromonas* resistant strains, making any antibiotic treatment ineffective in several fish such as catfish, koi carp and tilapia [122]. Furthermore, most antibiotic resistance studies have been conducted on these pathogens because of their unusual biofilm formation and antibiotic resistance [123]. The first fish pathogen reported that showed antimicrobial resistance was *A. salmonicida* and was resistant to tetracycline and sulfathiazole [124]. Jacobs and Chenia (2007) observed high levels of resistance to tetracycline (78.3%), amoxicillin (89.2%) and augmentin (86.5%) in *Aeromonas* isolates from trout, tilapia and koi from South African aquaculture systems [125]. *A. hydrophila* and *A. salmonicida* isolates exhibited higher resistance levels to different antimicrobial agents when compared with *Aeromonas encheleia*, *Aeromonas popoffii*, *A. veronii*, *Aeromonas media* and *Aeromonas ichtiosoma* isolates [125]. This is likely because large amounts of antibiotics, such as oxytetracycline, quinolones and trimethoprim, have

been used over the years to treat furunculosis in infected salmonids [126]. In the last two decades, there has been an increase in reports of quinolone resistance among fish-associated aeromonads [10,127–129].

Vaccination is an alternative and feasible control method to prevent *Aeromonas* sp. infections; however, the vaccines available in aquaculture are still very limited. Vaccines have been successfully used in aquaculture, reducing the use of antibiotics, particularly in salmon production [39]. In aquacultures, the most currently used vaccines are inactivated vaccines since this present greater biosafety and are easier to license [130]. Live or attenuated vaccines have shown great potential, achieving fish immunization with a single dose and having low production costs [20,131]. However, the use of live bacteria poses a threat to the environment and therefore, few of these are licensed for commercial use [130,131]. Currently, over 26 fish vaccines are licensed and commercially available for use in various fish species [6,17–20] and have successfully protected fish against several fish diseases [20]. Most licensed vaccines contain inactivated microorganisms and adjuvants that can be delivered through immersion or by injection [20,130]. Unfortunately, vaccines for many farmed fish species and pathogenic bacteria have not been developed [39]. Duff (1942) was the first to report the application of vaccines against *A. salmonicida* in cutthroat trout, *Oncorhynchus clarki*. In these trials, the fish were fed inactivated *A. salmonicida* [132]. The development of the first salmonid vaccines that were delivered by immersion used the same bacterial inactivation principle applied in the Atlantic salmon (*S. salar*) [133]. However, these injection-based bacterial vaccines were not effective against *A. salmonicida* in Atlantic salmon as Bricknell and colleagues reported [134]. In this study, the extracellular polysaccharide vaccines induced an antibody response and were protective for about 2 months following injection [134]. In the last few years, several vaccines against typical *A. salmonicida* strains were developed to provide long-lasting protection in commercial salmonid culture [55,135]. In 2011, China granted the national class I new veterinary drug certificate to a killed whole-cell vaccine for *A. hydrophila* (J-1 strain), the first aquatic bacterial vaccine for this species [136]. AQUAVAC® FNM is a non-mineral, oil-based injectable vaccine that contains two strains of *A. salmonicida*, the causative agent of furunculosis in Atlantic salmon [137]. Alpha Ject Panga 2 was approved in 2017 in Vietnam. The Alpha Ject Panga 2 is an injectable vaccine that protects against *A. hydrophila*, and *Edwardsiella ictaluri* [138]. DNA vaccines using carbon nanotubes or those that are yeast-based have, similar to inactivated vaccines, recombinant protein vaccines and bacterial lysates, demonstrated to stimulate protection against *A. hydrophila* [131,139–142]. The development of commercial vaccines against *A. hydrophila* in fish has been challenging because of its biochemical and serological heterogeneity [143]. Despite vaccination representing an effective strategy to prevent *Aeromonas* infections, these have been linked to a variety of side effects such as impaired growth, inflammation, fibrous adhesions in internal organs, scarification and pigment deposition [144–147]. Moreover, vaccines require developed and functional immune systems which, in larval or fry stages, will have low to poor outcomes [23]. Furthermore, they do not always offer full protection and can be very difficult to administer by injection [6]. As such, the application of virulent phages to prevent and/or treat infections appears as a promising strategy [51,91,94,148–150], at a time when more efficient approaches are needed to control *Aeromonas* diseases.

4. Therapeutic Application of Phages

Phage therapy uses phages, viruses that only infect prokaryotes (bacteria and archaea) [151,152], to inactivate pathogenic bacteria. They do not possess host-independent metabolism and cannot produce proteins, as such, are incapable of self-replication [153–155]. Phages were discovered independently by Frederick W. Twort in England in 1915 and by Felix d'Herelle in Paris in 1917 [156]. However, their phage application ideas were later abandoned by Western European countries due to the success of antibiotics [32,157]. It was only in recent decades that its interest was regained following the growing concern with antimicrobial resistance [32,42]. The emergence of pathogenic bacteria resistant to

antibiotics has recently motivated the Western scientific community to re-evaluate phage therapy for the treatment of bacterial infections. To do so, several aspects of phage ecology, namely, abundance, viral decay rates, repair mechanisms, lysogeny and impact on bacterial communities, need to be further understood [158,159]. Since the regulatory acceptance of ListShield™ [produced by Intralytix Inc (Baltimore, MD, USA)], the first phage-based product (a cocktail of six different virulent phages approved to control *Listeria* in meat and poultry products), the amount of research and development of new phage-based technologies for pathogen control has increased [37,160]. Currently, the potential use of phage therapy in medicine [33,44,154,161,162], aquaculture [2,38–41,51,52], food safety [32,34,36,37,163–166], agriculture [34,35,167–170], veterinary [45,46,48] and wastewater treatments [171,172] has started to be studied worldwide.

As soon as they were discovered by Twort and d'Herelle in the early 1920s, phages were described as antibacterial agents for both humans and animals [173]. More than fifty years later, studies were also initiated using phages to control pathogenic bacteria in aquaculture. Following the first reported application of phages to control *A. hydrophila* in aquaculture, in 1981 [174], several virulent phages that infect the main bacterial pathogens present in aquacultures, such as *Aeromonas* spp., *Edwardsiella* spp., *Flavobacterium* spp., *Pseudomonas* spp. and *Vibrio* spp. [92,175–189] were isolated and characterized for potential therapeutic. Recent studies focused on the isolation and characterization of lytic phages, cocktails [95,150,184,185,190–193] and addressed the potential application of phages as a therapeutic agent to control diseases in aquaculture, their dosage and administration [194].

The prophylactic application of phages has been effective in treating *Edwardsiella tarda*, a bacterium that causes edwardsiellosis in loach *Misgurnus anguillicaudatus* [195]; *Lactococcus garvieae* causing lactococcosis in yellowtail *Seriola quinqueradiata* [196]; *Pseudomonas plecoglossicida* causing pseudomonosis in *Plecoglossus altivelis* [197,198], *Flavobacterium psychrophilum* and *Flavobacterium columnare* causing flavobacteriosis in *O. mykiss* [3,194,199,200]; as well as *Vibrio parahaemolyticus* and *Vibrio splendidus* infections in sea cucumber *Apostichopus japonicus* [192,201]. Other successful studies have previously reviewed phage therapy in aquaculture [2,39,40,202].

Over the last couple of years, few companies invested in phage-based solutions to control and/or prevent bacterial infections in aquaculture, as seen in the small number of products developed so far (Table 2).

Table 2. Companies involved in the development of phage-based products to control or prevent bacterial infections in aquaculture.

Company	Country	Target Application	References
Intralytix Inc.	Baltimore, MD, USA	Phage-based application to fight *V. coralliilyticus* and *V. tubiashii* infections in hatchery-raised oysters	[203]
BASF New Business GmbH	Ludwigshafen, Germany	Products that mix phages covalently to particles into the feed to treat infections caused by *Vibrio*, *Yersinia*, *Aeromonas*, *Rickettsia*, *Moritella*, *Lactococcus*, *Piscirickettsia*, *Flavobacterium*, *Pseudomonas*, or *Photobacterium*	[204]
Proteon Pharmaceuticals S.A.	Łódz, Poland	Natural feed additive called BAFADOR® that can control bacterial infections caused by *Pseudomonas* spp and *Aeromonas* spp. serotypes in commercial aquaculture	[50]
Fixed Phage Ltd.	Glasgow, Scotland	Phage particles immobilized in pellets that can be added to fish and crustacean feed to treat bacterial infections in aquaculture, including Early Mortality Syndrome in shrimps and *Flavobacteria* infections in salmonids	[204]

Table 2. *Cont.*

Company	Country	Target Application	References
ACD Pharma	Oslo, Norway	Phage-based solutions against several aquaculture pathogens; CUSTUS® YRS is a product that reduces the infective pressure from *Y. ruckeri* in aquaculture water	[205]
Mangalore Biotech Laboratory	Karnataka, India	A product called LUMI-NIL MBL prevents and treats *Vibrio harveyi*-caused luminous vibriosis	[206]
Phage Biotech Ltd.	Rehovot, Israel	Phage treatment for *V. harveyi* in aquaculture shrimps	[202]
Biologix	Australia	Phage treatment for *Vibrio* sp. associated with mortalities in aquaculture	[207]
Aquatic Biologicals	Greece	Phage treatment against several pathogens associated with mortalities in aquaculture	[208]

5. Application of Phages Infecting *Aeromonas* sp. in Aquaculture

Aeromonas species are recognized as the third most targeted aquatic bacterial pathogen in phage application research [39] and were the first target for phage therapy in aquaculture back in 1981 [174]. These authors isolated eight *A. hydrophila* phages from which AH1 was selected for the study of biological control of disease in loach *M. anguillicaudatus*. The authors injected the loach *M. anguillicaudatus* with *A. hydrophila* and observed that, after 3 h of phage treatment, the bacterium had completely lost its infectivity and mortality halted in the phage inoculated animals. Even at a multiplicity of infection (MOI) of 0.001, infectivity and mortality were reduced to 40% of uninfected *A. hydrophila* [174]. Since then, several studies have evaluated and shown the promising results that some *Aeromonas* phages have as alternative biocontrol agents and their therapeutic (or prophylactic) potential in aquaculture. However, studies with phages aiming to prevent or eliminate *Aeromonas* spp. in aquaculture have been restricted to two pathogenic bacterial species so far, *A. hydrophila* and *A. salmonicida (*Tables S2 and S3).

Several studies have analyzed phenotypic and genotypic characterization, and evaluated the effectiveness of phages against *A. hydrophila*, including phages pAh1-C and pAh6-C [209]; Ahp1 [210]; pAh-1 [211]; Φ2 [95]; AP1, AP2, AP3 and AP4 [92]; CT45P and TG25P [212]; MJG [91], AHP-1 [181]; Akh-2 [149], PVN-02 [148,213], AhyVDH1 [214] and pAh6.2T [94] (Tables S2 and S3). Previous studies have shown that phages can be used to biocontrol *A. hydrophila* infections in loach (*M. anguillicaudatus*) [149,174,209], Nile tilapia (*O. niloticus*) [92,93], striped catfish (*P. hypophthalmus*) [95,148] and rainbow trout (*O. mykiss*) [91,94] (Table S3).

The first application of phages to control *A. hydrophila* in loach occurred in 1981 [174]. More than three decades later, Jun et al. (2013) showed that a single administration of simple suspensions of phages pAh1-C or pAh6-C increased survival rates against *A. hydrophila* infection. However, phage pAh6-C controlled *A. hydrophila* infection more effectively than phage pAh1-C [209]. Recently, Akmal and colleagues showed the protective effects, with increased survival rates (0–43%) and mean times to death in *M. anguillicaudatus* infected with *A. hydrophila* [10^7 colony-forming units (CFU)/mL)] and treated with phage Akh-2 [10^8 plaque-forming units (PFU)/mL)] [149]. The protective effect of *Aeromonas* phages to control *A. hydrophila* in Nile tilapia (*O. niloticus*) was also reported by [92,93]. El-Araby et al. (2016) applied a mixture of two phages by immersion to control *A. hydrophila* in Nile tilapia (*O. niloticus*) and reduced the mortality rate from 68% to 18% after a 15-day treatment. In another study, Hassan et al. (2018) showed the promising effect of phage AP2 to treat motile *Aeromonas* septicemia induced by *A. hydrophila* in Nile tilapia [92]. Only very recently, with Le et al. (2018), have phages been investigated for their potential to prevent and treat bacterial diseases in catfish (*P. hypophthalmus*). Namely, the ability that phages Φ2 and Φ5 have to inactivate and control *A. hydrophila* in striped catfish by

injection and the observed cumulative mortality of fish decreases with the increase in MOI (cumulative mortality of 0%, 45% and 68% with an MOI of 100, 1 and 0.01) [95]. Dang and co-workers had similar results and observed that fish mortality depends on the phage dose used during treatment [148]. However, the difference is not so great, as that observed in Le et al. (2018) [95]. Dang et al. (2021) demonstrated that the relative survival percentage of catfish with *A. hydrophila* was 75.6–87.8% when fed with phage PVN02-sprayed feed [148]. Cao et al. (2020) administered phage MJG by injection, immersion and oral administrations to control *A. hydrophila* in rainbow trout and achieved a relative percent survival of 100%, 66.7%, and 50%, respectively [91]. Additionally, Dien et al. (2021) showed that treatments with phage pAh6.2TG significantly improved survivability of Nile tilapia exposed to lethal doses of *A. hydrophila* (10^7 CFU/mL), with relative percent survival of 73.3% and 50% at an MOI of 1.0 and 0.1, respectively [94].

Several studies have shown the antimicrobial efficacy of different phages (including phage cocktails) to biocontrol *A. salmonicida* strains in vitro and/or in vivo experiments [51,150,180,215–219] (Tables S2 and S3). Among them, therapeutic (or prophylactic) applications of phages to control *A. salmonicida* in brook trout (*Salvelinus fontinalis*) [218], Atlantic salmon (*S. salar*) [219], rainbow trout (*O. mykiss*) [220] and Senegalese sole (*Solea senegalensis*) [51] (Table S3). Although Verner-Jeffreys et al. (2007) did not find any protective effects against *A. salmonicida* in Atlantic salmon treated with the mixture of phages O, R and B [219], three other studies showed clear differences between the phage-treated and control groups [51,218,220]. Imbeault et al. (2006) showed that phage HER110 delayed the onset of furunculosis by 7 days with fish mortality rates reducing from 100% to 10% after 45 days [218]. In 2015, Kim and colleagues showed notable positive effects, with increased survival rates (0–26%) and mean times to death in rainbow trout infected with *A. salmonicida* subsp. *salmonicida* (2.5×10^2 CFU/fish) and treated with phage PAS-1 (2.4×10^6 PFU/fish) [220]. The same was also verified in Senegalese sole (*S. senegalensis*) treated with phage AS-A, showing a significantly reduced mortality (36% to 0%) [51].

From the existing alternatives, phages have shown their potential to control *A. hydrophila* and *A. salmonicida*, but with some limitations. Their advantages and limitations in aquaculture have been thoroughly described in previous reviews [2,38–40,202,221]. Nevertheless, in this review, we highlight the major challenges phage application for *Aeromonas* sp. biocontrol face in the aquaculture industry and how they can be overcome.

6. Challenges Associated with the Use of Phages to Control *Aeromonas* sp.

Aquaculture studies have shown that phage therapy can grant fish overall protection and provided us with an optimistic outlook on the benefits that these phage-based technologies have to treat diseases in aquaculture. However, this therapy is still mostly in an early stage and needs to be further studied and described. Several studies have reported the isolation and characterization of new phages (Table S2) and their efficiency to control *A. hydrophila* and *A. salmonicida* (Tables S2 and S3); however, they are mainly in vitro with few reporting in vivo studies (Table S3). One of the issues facing the study of phage therapy is the ability to demonstrate its viability in vivo and in field conditions [51,52,198], because, in vitro assays are not enough to understand phage–bacteria interactions that occur in vivo.

While it is known that page therapy can prevent and treat infectious diseases, a few constraints may still hamper its application in aquaculture. Phage therapy requires a detailed understanding of bacteria–phage kinetics, time, phage and dosage, and application methods (e.g., oral administration through feed, injection or immersion). Some phage advantages (such as the narrow host range) can become drawbacks when designing phage therapy and should be well understood. Additionally, their ability to survive under environmental conditions is highly diversified, which makes it important to understand the complex problem of phage sensitivity to external abiotic factors (such as salinity, temperature, pH and UV radiation).

Several studies still overlook phage genome sequencing. The knowledge of how the natural mechanisms contribute to the emergence of phage-resistant bacteria and which

bacterial receptors may be specific to a phage is crucial for the successful application of phages in aquaculture [222].

In addition, despite certification by the regulatory entities, the stigma producers and consumers have regarding phage safety must be addressed and overcome [207]. While the scientific interest regarding the industrial application of phages has been rising, few are the private companies that have followed the trend, started working on or have launched, phage-based technologies for aquaculture [39]. Therefore, additional efforts are needed to assess producer and consumer understanding, followed by educational campaigns to raise awareness and acceptance of phage application in aquaculture.

6.1. Phage Selection

The selection of appropriate phages is one of the main steps required to achieve successful phage-mediated control of pathogenic bacteria. The key pre-requisites during preparation and selection of phage suspensions to be used in phage therapy, include (i) lytic activity (only virulent phages should be used), (ii) host range, (iii) adsorption rate, (iv) growth parameters (burst size and latent period), (v) environmental stability, (vi) bacterial inactivation efficiency and (vii) safety [2,32,152,190,223].

Phages are non-toxic and there is little evidence of harmful phage immune responses. Nonetheless, it is still crucial that phage preparations are pure and free of bacterial components [224].

During phage isolation from environmental sources, only virulent phages should be selected for therapeutic application. Temperate phages should not be used in phage therapy [225] because they can grant the host immunity against the same or similar phages. The bacterial host can acquire new genetic traits like phage-encoded toxins and antibiotic resistance determinants by phage conversion since phages will easily convert the bacterial hosts into lysogens (phage-resistant), thus rendering them unable to cause immediate lysis [155,225]. Lysogenic conversion may be detected by the presence of enzyme-encoding genes (such as integrase or ParA/B genes) in the genome [84,217,218]. Moreover, when selecting a phage, their potential to transfer virulent genes or other phage toxic factors between bacteria (transduction) must also be evaluated and taken into consideration [152]. If phages are to be used as therapeutic agents, their safety should be evaluated at the genome level, and phages with lysogenic conversion-related genes (such as integrase or ParA/B genes) or potentially damaging genetic determinants (toxins or antimicrobial resistance genes) should be excluded before further experiments [226,227].

6.1.1. Phages Specificity

A major limitation of phage application is its narrow host range and geographical specificity [39,228,229]. In general, phages are highly specific, infecting only one bacterial genus or even particular strains [224]. Most *Aeromonas* phages showed narrow host specificity, infecting only the original host bacterium [51,93,150,214] or strains of a given bacterial species [91,94,95,149,209,220,230,231] (Table S2). The majority of marine phages are highly host-specific [232–234], and about 73% lyse only the original host bacterium [234]. Although phages with a broad host range are hard to find, some examples of virulent phages have shown some promise for therapeutic use in aquaculture, infecting strains of several bacterial species [180,181,217,235,236] and genera [92,237] (Table S2). Liu et al. (2020) reported that the isolated phages had a relatively broad infectivity spectrum against *A. hydrophila* and showed the potential to infect *A. veronii*, *A. caviae* and *A. bestiarum* [236]. In 2011, our research group showed that phage AS-1 infected, beyond the host, *V. anguillarum* and *V. parahaemolyticus* (efficacy of 98.87% and 96.03%, respectively) [237]. In another study, phages AP-1, AP-2, AP-3 and AP-4 showed a broad host range to other genera [92] (Table S2).

Aquaculture environments contain a wide variety of *Aeromonas* sp. that are pathogenic to fish, which hinders the inactivation effects of a single narrow-spectrum phage. Phages that cover a wide spectrum of bacteria are usually in the research area of interest. However,

even phages with the broadest host spectrum cannot infect all pathogenic bacterial isolates because of coevolution between bacteria and phage [238]. To overcome this problem, phage cocktails, containing multiple phages that target several possible pathogens, can be used and thus extend their action range [239,240].

6.1.2. Adsorption Rate

Phage adsorption rate may be critical for treatment success. Higher adsorption rates should result in higher phage propagation [241,242]. Storms and colleagues observed that an increase in adsorption efficiency had a similar effect as an increase in the initial MOI; however, the number of phages produced during the amplification phase decreased [243]. Phage AHP-1 adsorption assays showed that approximately 81.5% of phage particles were adsorbed to *A. hydrophila* after 25 min, with an adsorption rate constant of 3.06×10^{-8} mL min^{-1} [181]. In other studies, *A. hydrophila* phage adsorption reached over 90% after 40 min [95], while El- Araby et al. (2016) showed a 51% and 66.8% adsorption after 20 and 30 min, respectively [93]. Phage Ahp2 showed a high adsorption efficacy with 96% of phage particles being adsorbed to *A. hydrophila* in the first 18 min [230]. Chen et al. (2018) reported that the five isolated phages (AS-szw, AS-yj, AS-zj, AS-sw and AS-gz) showed strong adsorption to *A. salmonicida* surface and approximately 90% (2.7×10^4 PFU/mL out of 3.1×10^4 PFU/mL) of phage particles adsorbed to *A. salmonicida* within the first 5 min [217]. Nithin et al. (2021) reported that phage AhFM4 showed more adsorption efficacy (96% adsorption within 30 min) when compared with phage AhFM5 (70% of phage was adsorbed within 30 min) [231] (Table S2). That is, phages with a higher adsorption rate should have shorter lysis and vice versa. Because with higher adsorption rates, phages encounter and attack the host more quickly and as such, have a shorter optimal lysis time when compared to phages with a lower adsorption rate.

6.1.3. Latent Period and Burst Size

The selection of phages with a low latent period (time elapsed since phage acid nucleic entry into the cell until the virion progeny are released) and high burst size (number of phage virions produced by each host cell) is very important [32]. A phage is considered a highly lytic phage when it has a short latent period and/or high burst size. Phages shouldn't be administered in high doses because they cannot diffuse properly. A high burst size not only increases the probability of phage particles reaching the target bacterial cells but also results in a lower risk of selecting phage-resistant bacteria if the phage can eliminate the bacteria faster than they can replicate [240]. Phages with a short latency period are more prevalent during isolation. As such, if they are present in high titer from the beginning, they should be selected for phage therapy because a phage with a long latency period and high burst size may never be found [240]. A phage's burst size depends mainly on its availability to the bacterial host cells and latent period, being the last affected by phage type, host and environmental conditions [244,245]. Phages with high burst sizes and short latent periods are expected to be more effective in controlling bacteria since these would be able to survive longer in the environment if it maintains their proliferation threshold [246]; however, some phages presenting high burst sizes have been accompanied by long latent periods [166]. Moreover, a rapid increase in phage particles can also contribute to phenomena such as "lysis from without" and other replication anomalies [247]. These can lead to premature cell lysis that hampers phage selection for phage therapy.

An extended latent period can increase phage burst sizes because more time is available for progeny maturation during infection [248]. Few reports, however, have shown high (608 PFU/infected cells) [211] and medium burst sizes (160–316 PFU/infected cells) with the same latent period [236].

Aeromonas phages have a wide range of latent periods and burst sizes, going from high burst sizes (608 PFU/infected cells) and short latent periods (15 min) [211] to low burst sizes (5 PFU/infected cells) and long latent periods (40 min) [150].

A. hydrophila phages vB-AhyM-AP1 and pAh-1 presented high burst sizes (1413 and 608 PFU/host cell, respectively); however, the latent period of phage vB-AhyM-AP1 (40 min) is higher than that of phage pAh-1 (15 min) [211,235] (Table S2). Phage AhyVDH1 infected *A. hydrophila* producing 274 PFU/host cell [214], TG25P (79 ± 11.9 PFU/host cell) [212]; Akh-2 (139 PFU/host cell) [149] and AHP-1 (97 PFU/host cell) [181]. The latent period of phage AhyVDH1 (50 min) is almost the same as of *A. hydrophila* phages TG25P (40 min) [212], AHP-1 (40 min) [181] and Akh-2 (50 ± 5 min) [149] (Table S2).

Chen et al. (2018) demonstrated that *A. salmonicida* infecting phages AS-szw, AS-yj, AS-zj, AS-sw and AS-gz had a burst size of 145, 98, 86, 86 and 135 PFU/host cell, respectively, with a latent period of approximately 40, 20, 20, 50 and 30 min, respectively [217]. In another study, phage ASP- 1 presented a low burst size of 16 PFU/host cell and a latent period of 30 min [180]. Similar results were obtained with virulent phages AS-A (22 PFU/host cell, 30 min), AS-D (5 PFU/host cell, 40 min) and AS-E (10 PFU/host cell), and that low burst size did not affect the growth reduction of *A. salmonicida* [150].

6.1.4. Phages Stability

To determine the effectiveness of phages, it is necessary to understand their stability under the influence of several parameters [32,150,224,249–252]. Phage stability may be influenced by several factors like solution composition (presence or absence of particular ions), production process parameters (e.g., temperature, pressure) or environmental conditions (e.g., temperature, pH, salinity and UV radiation) [32,224].

In aquaculture, phages are exposed to the natural variation of environmental conditions, such as temperature, salinity, pH and UV radiation. Some studies showed that phage stability can be negatively affected by those environmental factors [150,249–252]. These factors can inactivate phage particles by damaging their structural protein elements (capsid, sheath, tail), lipid loss, and/or promoting DNA or RNA structural changes [253]. Phage stability is highly variable, tailed phages are the most stable in adverse conditions and phages with larger capsids have higher survivability [250,253].

Temperature and pH in aquaculture waters are usually moderate and may not influence phage activity; however, the production and formulation process parameters might not be as mild [252]. Therefore, for effective production, it is better to choose phages that are stable at different temperatures and pH.

Temperature is a fundamental factor for virulent phage stability [150,252,254–256], playing a crucial role in attachment, genome injection and phage multiplication [250]. At low temperatures, only a small amount of phage particles injects their genetic material into the host cell, as such, few are involved in the amplification phase [257]. On the other hand, the latent period can be prolonged with higher temperatures [257] and degrade the proteins that built up the capsid [224]. Some studies proved that thermal stability is specific for each phage and is different depending on the phage isolate. Phage ASP-1 was stable at high temperatures (4–50 °C) for 1 h [180] but, the viability of phages φZH1 and φZH2 decreased at temperatures above 40 °C [93]. Cheng et al. (2021) reported that phage AhyVDH1 was thermostable at 30 °C and its survival rate decreased to about 66.7% at 40 °C after 60 min, and it was inactivated at 50 °C after 20 min [214]. In another study, Chandrarathna et al. (2020) observed that phage AHP-1 can survive temperatures ranging between 4 °C and 50 °C, even though the infectivity decreased by 75% at 50 °C [181] (Table S2).

Phage stability is also influenced by the acidic and alkaline nature of the environment [250], which affects attachment, infectivity, intracellular replication and phage multiplication [258–260]. Adverse pH can inhibit the lysozyme enzyme and the phage protein coat, thus affecting the adherence to the host cell [258]. Due to their protein nature, phage survival usually slowly decreases with environment acidification, promoting their coagulation and precipitation [250]. Generally, the phage lytic activity decreases in pH values ranging between $10 < pH < 5$, with optimum pH conditions around neutrality (pH of 6–8) [196,260]. Several phages isolated for *A. salmonicida* and *A. hydrophila* control and presented in Table S2 can tolerate a wide range of pH values, namely phage AS-D

(pH 5.5–8) [150], phages AS-yj (pH 5–10) and AS-gz (pH 4–11) [217], phages CT45P and TG25P (pH 5–9) [261], phage ASP-1 (pH 4–11) [180], phage Akh-2 (pH 7–9) [149], phage AhyVDH1 (pH 5–10) [214], phage PVN02 (pH 7–9) [148], phage pAh6.2T (pH 7–11) [94], phage AHP-1 (pH 7–10) [181], phage vB-AhyM-AP1 (pH 5–10) [235], phage pAh-1 (pH 5–11) [211], phages N21 (pH 5–11), W3 (pH 4–10), G65 (pH 4–11), Y71 (pH5–10) and Y81 (pH 4–10) [236], and phages AhFM4 and AhFM5 (pH 5–8) [231].

Phage particles require salts at low concentrations to successfully infect the bacteria and multiply [262]. At low concentrations, salt ions stabilize proteins by neutralizing their charges [256]. At higher concentrations, thermal denaturation of proteins occurs and the structural stability of the phage's nucleic acid can be affected [263]. *A. salmonicida* phage AS-D remained stable at salinity concentrations of 15%, 20% and 35% for 49 days, after which a decrease of about three orders of magnitude until the 107th day occurred [150]. Phages isolated to control *A. hydrophila* can tolerate a wide range of salinity concentrations, namely phage ASP-1 (0.1–3.5%) [180], phage vB-AhyM-AP1 (0.1–2.0%) [235] and phages AhFM4 and AhFM5 (0.5–2.0%) [231]. Phage pAh6.2TG was relatively stable at a wide range of salinity concentrations (0–40%) for 24 h [94] (Table S2).

UV radiation is one of the main factors that affect phage particle stability in surface coastal waters [150,255,264–267]. This radiation can degrade phage proteins and form photoproducts such as cyclobutene pyrimidine dimers [268,269], and/or modify their genetic material (either DNA or RNA) [150,264–267]. Since lethal UV radiation photoproducts are normally thymine dimers, DNA phages are usually more sensitive to damage than RNA phages [256]. Besides, phages with double-stranded genomes are more resistant to UV radiation than single-stranded ones [270–274]. However, our research group observed that AS-D, a double-stranded DNA phage, was able to tolerate UV-B radiation (290–320 nm) while decreasing only by 1.3 log PFU/mL after exposure for 24 h [150]. Phages ΦZH1 and ΦZH2 tolerated UV irradiation, losing 50% of its infectivity after a 100 min and 80 min exposure time, respectively [93].

6.2. Multiplicity of Infection (MOI)

The MOI value is an important factor in phage therapy efficiency, it changes depending on the animals, pathogens and phages used in in vivo experiments because of the complex physicochemical environment, host defenses and the outcome in in vitro assays [32,39]. In large-scale production and commercialization of phage products, it would be advantageous and even preferable that phages would be applied in low titres to reduce preparation, purification and application costs [32].

Some authors showed, both under in vitro and in vivo conditions, that the bacterial inactivation occurs in parallel with the MOI or that inactivation occurs earlier with higher MOIs [94,95,180,181,214]. Le et al. (2018) observed that the increase in MOI from 0.01 to 100 promoted a significant increase in the striped catfish survival (*P. hypophthalmus*) [95]. These authors used phage cocktails (phages Φ2 and Φ5) with an MOI of 0.01, 1, and 100 to control *A. hydrophila* infection in striped catfish by injection and obtained relative percent survival of 16.33%, 44.9%, and 100%, respectively. Similar results have been observed for other phages [94]. Treatments with phage pAh6.2TG significantly improved Nile tilapia survival when exposed to lethal doses of *A. hydrophila*, with relative percent survival of 73.3% and 50% for MOIs of 1.0 and 0.1, respectively [94]. Cheng et al. (2021) reported that a higher phage dosage (MOI of 10) had a higher effect on *A. hydrophila* reduction [214]. Similar results were noted by other researchers for phages ASP-1 and AHP-1 against *A. salmonicida* and *A. hydrophila* strain, respectively [180,181]. However, Chen et al. (2018) observed that phage-resistant bacterial variants may be induced more rapidly by heavy phage concentrations than those treated with lower concentrations. These authors showed that bacterial density (OD600) rapidly increased when incubated with higher MOIs (10 and 1), even though bacterial inactivation occurred earlier than at lower MOIs (0.1 and 0.01) [217]. Similar results were obtained by Jun et al. (2013) for phage pAh6-C against *A. hydrophila* [209].

6.3. Administration Routes

The route and time of application are other factors that influence phage therapy efficiency. In aquaculture, phage delivery can be done through immersion, injection, within the feed, and topical application. The phage-impregnated feed is more appropriate in prophylactic efforts as infected fish may not consume their food [275]. The selection of the right application method is essential; however, each biological system is different and should be considered independently [224]. Whatever the application method, it is important that the phages particles contact the bacterial host, either in water, on the surface or inside fish [275]. This can be easily achieved in fish tanks by maintaining water circulation through pumps or extensive fish mobility in high-stocking tanks [275].

Immersion in seawater tanks is the most common technique used in phage therapy studies to control *Aeromonas* sp. in fish [51,91–94,149,209,218,219,276] (Table S3). Treating loach (*M. anguillicaudatus*), rainbow trout (*O. mykiss*), Nile tilapia (*O. niloticus*), brook trout (*S. fontinalis*) and Senegalese sole (*S. senegalensis*) by immersion could provide significant protective effects against *A. hydrophila* infection [51,91–94,149,209,218,276]. However, due to *A. salmonicida* subsp *salmonicida* high infectivity, even at extremely low concentrations, in Atlantic salmons, phage treatment by immersion was ineffective in preventing or treating the pathogen [219].

Some studies reported phage protective effects against *A. hydrophila* and *A. salmonicida* infection by intraperitoneal injection [91,95,209,211,219,220,277] (Table S3). Le et al. (2018) reported that intraperitoneal injections in catfish provide significant protective effects, with their survival rate increasing when the MOI value increased [95]. In another study, the administration of phage PAS-1 in a rainbow trout model infected with *A. salmonicida* subsp. *salmonicida* showed notable protective effects, with increased survival rates and delayed death by almost 1 day [220]. A dissimilar result was achieved by Verner–Jeffreys et al. (2007), who showed that no protection was offered by intraperitoneal injection of phages O, R and B, compared to the positive challenge group [219]. The labour-intensive and time-consuming administration of phages by intraperitoneal injections can constitute a disadvantage for fish treatment in catfish farms.

Some reports compare different methods of phage administration. Jun et al. (2013) evaluated the protective effects of intraperitoneal injection and oral administration of phages pAh1-C and pAh6-C against *A. hydrophila* [209]. In this study, the fish were infected with two different bacterial concentrations (10^6 CFU/fish and 10^7 CFU/fish) and treated with phages phAh1-C and phAh6-C (10^7 PFU/fish). The fish treated with phages by intraperitoneal injection and oral administration showed lower mortality rates than the control group. In fish infected with 10^6 CFU/mL of *A. hydrophila* and treated by intraperitoneal injection, no mortality was observed in the groups treated with phages pAh1-C or pAh6-C over 7 days (cumulative mortalities in the control group was $39.17 \pm 3.82\%$). However, when the fish were infected with 10^7 CFU/mL, the cumulative mortality was $43.33 \pm 2.89\%$ for phage pAh1-C and $16.67 \pm 3.82\%$ for phage pAh6-C (cumulative mortality in the control group was 100%) [209]. When the fish were infected with 10^6 and 10^7 CFU/mL of *A. hydrophila* and fed with phage-coated food the cumulative mortalities were $17.50 \pm 2.50\%$ and $46.67 \pm 3.82\%$ for phage pAh1-C and $11.67 \pm 3.82\%$ and $26.67 \pm 2.89\%$ for phage pAh6-C. The cumulative mortalities in the control group were $38.33 \pm 2.50\%$; 2nd trial, $95.83 \pm 3.82\%$ [209]. Cao et al., in 2016, published a report in which they described the use of phage MJG to control *A. hydrophila* in rainbow trout (*O. mykiss*) [91]. The fish were infected with *A. hydrophila* (10^8 CFU/fish) and treated with a single dose of phage MJG (3.2×10^6 PFU/fish) administered intraperitoneally 2 h post-bacterial infection or immersed in water for 15 min with phage at a concentration of 3.2×10^6 or 3.2×10^5 PFU/mL. Phage MJG injection completely protected the fish from *A. hydrophila* infection (cumulative survival in the control was 40%). In the immersion treatment, the cumulative survival was 100% and 80% with phage concentrations of 3.2×10^6 PFU/mL and 3.2×10^5 PFU/mL, respectively [91].

Another very important factor for the success of phage therapy is the time of administration. This parameter is highly dependent on the type of disease and how advanced the infection is. Verner-Jeffreys et al. (2007) observed that Atlantic salmon injected with the phage cocktail (phages O, R and B), immediately after bacterial inoculation, died at a significantly slower rate than those without phage treatment or treated 24 h after inoculation [219].

A phage's ability to cross the epithelial barrier or withstand gastric conditions determine how it can be administrated. These parameters may impact phage degradation in the gastric tract and may decrease phage therapy effectiveness [278]. To avoid these problems, coatings can be applied to fish feed containing phages [279]. The edible whey protein isolate coatings loaded with phages enhance fish treatment by reducing phage activity loss. Results from a simulation assay for gastric-intestinal digestion showed that this method enhances phages stability and reduces bacterial levels. Furthermore, it allows to control phage release in saltwater and protects them until they reach their destination [39,278].

6.4. Bacterial Resistance

Phage-resistant bacteria is probably the major concern regarding phage therapy, which could jeopardize favorable treatment outcomes. During treatment, some mutations will spontaneously occur and phage-resistant bacteria will regrow. However, most of these experiments are performed in a nutrient-rich medium without the presence of competition [150,166]. In these studies, since the remaining viable bacteria are not challenged by the host's immune system and the culture conditions are suitable for bacterial growth, resistant bacteria can regrow to concentrations similar to those of the non-treated control [150,166]. Our research group obtained similar results in vitro; however, the same didn't happen in vivo, where the phage-resistant bacterial mutants were at lower concentrations than the susceptible bacterial population [51].

Phage-resistant bacteria can develop from (i) alteration or loss of bacterial cell surface receptors; (ii) receptor(s) blockage by the bacterial extracellular (exopolysaccharide) matrix; (iii) inhibition of phage DNA penetration; (iv) production of modified restriction endonuclease enzymes that effectively hydrolyze phage DNA; or (v) inhibition of intracellular phage assembly [280]. Of these, changes in bacterial cell surface phage receptors represent the most frequent cause of resistance [280,281].

The use of phage cocktails during phage treatment may help overcome the problem of bacterial phage resistance. However, its success requires phages that do not have overlapping cross-resistance, i.e., bacterial mutants resistant to one phage but still sensitive to the other, and vice versa [39], using, for instance, phages from different families. Therefore, cocktails made of phages that only target bacterial lipopolysaccharides, for example, should be less successful than cocktails containing phages that target different receptors. Furthermore, the different phages should be able to be adsorbed onto the bacterial cell surface and have their genome injected. On the other hand, the different phages may interfere with each other upon co-infection, which is problematic [246]. However, phage cocktails do not prevent the emergence of phage-resistant mutants [150,166,212], although they can limit the development of resistant bacteria [166]. In one study, the frequency of *A. hydrophila* mutants resistant to phage AH-1 (3.10×10^{-3}) and AH-4 (1.14×10^{-3}) was higher than that observed with the phage cocktails (8.26×10^{-4}) [166]. However, in another study, the rate of phage-resistant bacteria to the phage AS-D (9.11×10^{-5}) was slightly lower than that observed with phage cocktails AS-A/AS-D (1.64×10^{-5}), AS-D/AS-E (1.05×10^{-4}) and AS-A/AS-D/AS-E (1.70×10^{-4}) [150]. As such, the combination of different therapeutic approaches should be considered to prevent and combat the emergence of microbial resistance. The combined treatment with phage AHP-1 and chloramphenicol (5 μg mL^{-1}) was more promising than individual treatments [181].

Several researchers have said that a small frequency of resistant mutants is not problematic and should not hamper phage application against pathogenic bacteria [282,283], and other authors stated that even bacterial exposure to phages could result in a "fitness

cost" for the bacteria [284,285] and contribute to their faster elimination from the environment when compared to their wild-type counterparts. In fact, our research group observed that colonies of phage-resistant bacteria were smaller and took several more days of incubation (5–6 days) to grow than the non-resistant bacterial colonies (24 h) [51]. These results indicate that phage-resistant bacteria tend to be less fit and, consequently, are expected to be eliminated from the environment more rapidly than their wild-type counterparts. However, this may vary across environments and the competition level for resources [286,287].

The specialty literature has stated that the phage itself can overcome the host's resistance through co-evolution [288,289] and our research group observed that after successive streak-plating steps, phage-resistant bacteria also mutated [290], with positive spot tests occurring only after the fourth and fifth steps. These authors confirmed these results by Fourier-Transform Infrared Spectroscopy (FTIR), where the spectra obtained from the fourth and fifth streak-plating colonies were similar to the ones from phage-sensitive control colonies, suggesting that these colonies are more similar to the control phage-sensitive bacteria than the colonies from streak-plating steps one, two and three [290].

6.5. Immune Response

A concern that hampers the success of phage therapy is the immunogenicity of phage particles. Phages can stimulate an immune response in fish, causing both specific or adaptative and non-specific or innate responses. The innate immune system reacts first by producing phagocytes to remove phages. The adaptive immune system enhances the first response with lymphocytes and antibodies. These systems work together, preventing viral attachment to bacteria, which can reduce or halt the therapeutic effect [249,291].

The existence of phage neutralizing antibodies before starting therapy or after repeated therapeutic administration might be a reason for phage therapy's failure [292]. High-titer phages usually stimulate the immune system of immunocompetent hosts [292]. However, antibody production depends on the route of phage administration, application timing and dosage, and the phage individual features [293]. The administration of *A. salmonicida* phage PAS-1 (MOI of 10000), in rainbow trout, showed significant neutralizing properties of its sera 10 days and 15 days after intramuscular administration which declined after 30 days [220]. However, this neutralization wasn't due to the presence of phage particles in the kidneys and occurred after the phage had been removed [220].

In a recent study, the immunogenicity of phages is highlighted as a profitable aspect. The authors used a phage lysate, composed of inactivated lytic phage pAh 6-c antigens to develop a vaccine for the prevention of *A. hydrophila* infection in *C. carpio*. Furthermore, to increase the effectiveness of the vaccine, the authors also tested the encapsulation of phage lysate and formalin-killed cells of *A. hydrophila* JUNAH strain with poly(lactic-co-glycolic acid) (PLGA) at low or high concentrations for intraperitoneal injection in fish [294]. Groups vaccinated with high doses of phage lysate antigen obtained higher agglutination concentrations than all other groups at 4-weeks and 6-weeks post-vaccination. Fish immunised with phage lysate vaccines had a higher survival rate than fish immunised with the formalin-killed cells vaccine. Vaccines with the phage lysate antigen also resulted in higher IL-1β and lysozyme C gene expression 7-days and 2-weeks post-vaccination, and higher TNF-α gene expression was seen 7-days post-vaccination. These results suggest that phage lysate antigen may induce stronger immune responses than formalin-killed cells-based vaccines and can be more effective as a novel inactivated antigen to prevent *A. hydrophila* infection in *C. carpio* [294]. Previous studies speculated that the phage's surface proteins can be recognized as foreign antigens by the host immune system and trigger stimulating immune responses. Moreover, it has been reported that, due to bacterial endotoxins such as lipopolysaccharides (LPS) and bacteria lysis remains, which may be in phage preparations or be produced by sudden lysis of many bacterial cells, an acute immune response can be induced [295]. In addition, serum TNF-α levels and the production of TNF-α and IL-6 by blood cells can be normalized by effective phage therapy [296]. However,

continuous exposure to the same phage can provoke adaptive immune responses with antibody production, which hampers the effectiveness of phage treatment [297].

Another challenge concerning phage therapy and the immune system response is the difficulty in reaching the site of infection in in vivo conditions. For phage therapy to be efficient, the amount of phage must be sufficient to reach the target bacterial cells [298]. According to Kalatzis et al. (2018), phage therapy in fish can make the adaptive immune system respond by eliminating phages from the body and preventing them from reaching the infection site [299]. The possible solution to overcome this issue is to study each case and choose carefully how to administer, the dosage, buffers and phage exposure time [300]. To protect phages when they enter the fish system, different approaches can be considered namely: phage microencapsulation, use of protective agents or appropriate buffers [249]. Screening phage mutants by genetic or chemical methods can also be used to reduce the immunogenicity of the surface proteins and thus prevent phages from being eliminated by the fish immune system so easily [301]. Furthermore, phage cocktails composed of different phages are desirable because they could help phage survival in living systems by neutralizing antibodies [249].

Phages possess strong immunomodulating and anti-inflammatory properties. The possible mechanisms responsible for these effects may involve LPS binding, inhibition of excessive production of reactive oxygen species and induction of IL-10 production [302]. Schulz et al. (2019a) studied the immunomodulatory activity of the commercially available phage cocktail designated BAFADOR®, a phage preparation against *A. hydrophila* and *Pseudomonas fluorescens*, in rainbow trout (*O. mykiss*), when a mixed infection of *Aeromonas* and *Pseudomonas* was induced [303]. For this, the authors determined the proliferative response of pronephros lymphocytes after stimulation with LPS or concanavalin A, as well as metabolic activity and potentially lethal activity of spleen phagocytes, total protein and total Ig contents, lysozyme and ceruloplasmin activities. Besides obvious antibacterial action against *A. hydrophila* and *P. fluorescens*, which decreased the mortality of rainbow trout, it also elevated immunoglobulin, lysozyme and protein levels, along with an increase in spleen phagocytes activity and pronephros lymphocytes proliferation [303]. The same group also studied the effect of BAFADOR® on the European eel (*A. anguilla)* immune system when a mixed infection of *Aeromonas* and *Pseudomonas* was induced [304]. Similar to the previous study, the results showed that BAFADOR® is well tolerated by the fish organism stimulating the parameters of cellular and humoral immunity and reducing the mortality of European eels after experimental challenge [304]. Cao et al. (2020) reported that the pro-inflammatory cytokines expression levels (IL-8 and IL-1β) were significantly higher in the spleen of phage MJG-treated fish than in PBS-treated fish 1- or 2-days post-infection but significantly lower in fish treated with PBS 3-days post-infection [91]. Therefore, phage treatment seemed to stimulate an early strong inflammatory response that weakened over time [91]. The proper inflammatory response removes harmful stimuli and restores health, but excessive and uncontrolled inflammation may damage the healthy tissues [305]. The strong inflammatory response may be associated with the release of endotoxins after cell lysis by phage MJG [91]. However, inflammation enhancement by phage treatment was significantly weaker than that by PBS treatment 3-days post-infection [91]. This may be explained by the low bacterial concentration and anti-inflammatory abilities of phage MJG [91]. Consistent with this result, phage MJG successfully restored tissue damage and eliminated any clinical signs of *A. hydrophila* infection in the fish [91]. In another study, Chandrarathna and co-workers verified that the immune gene expression of zebrafish upon continuous bath exposure to phage AHP-1 was significantly high (il-6 and sod-1) or slight (tnf-α, il1-β, il-10, and cxcl-8a) than the controls at the beginning of phage exposure. However, those values lowered to minimum levels 12 days after post-phage exposure, suggesting no adverse immune responses had occurred for the phage AHP-1 dose used, and potential for phage therapy [181].

6.6. Phage's Environmental Influence

Virulent phages are usually highly specific to a single species or even strain of bacteria and therefore, presumably, cause much less damage to the natural non-target bacterial communities and the normal intestinal fish flora. Though, as non-pathogenic bacteria have an important ecological role in aquatic systems, such as aquaculture systems, the effects of phage infection on bacterial communities in aquaculture water must be evaluated before applying phage therapy.

Phage therapy in the aquaculture system may have an impact on the environment by disrupting the microbiome [224]. Phages regulate the number of certain bacteria in a given environment and consequently change the bacterial proportions in that community [224]. Phages also have an important impact on the global biosphere organic matter cycle by releasing organic compounds through bacterial cell lysis [306]. Knowledge about these factors is especially important in the aquatic environment because it allows for rapid dissemination and acts as a vector for phages [39].

The likelihood of disruption to environmental bacterial communities can be reduced by using smaller phage doses. However, if phages are introduced in a small quantity, their concentration might be ineffective to control the pathogenic bacteria [39,224]. On the other hand, phages can reproduce and spread in the environment, not just in the targeted aquaculture system [239,307]. Despite being harmless, it is important to test their impact on the treated microbial community before any industrial-scale application.

Our research group evaluated the impact of phage AS-1 (*A. salmonicida* phage) on the bacterial community structure of an aquaculture system and observed a moderate impact on the overall bacterial community despite a broad host range [237]. In 2016, we also reported the impact of phage AS-A on natural bacterial communities of an aquaculture system and bacterial community associated with fish intestinal tract [51]. We observed that the addition of phage AS-A to the aquaculture water only significantly affected the bacterial community of the fish's intestinal tract and not the natural structure of the bacterial community [51].

7. Conclusions and Future Perspectives

Currently, the effectiveness of antibiotics is faltering as more and more antibiotic-resistant strains are identified. As such, alternative treatments such as phage therapy should be explored. Most of the studies reviewed in this paper showed the effect phages have in the control of *Aeromonas* species on fish, thus providing a positive outlook on the future benefits of this technology to treat aquaculture diseases. However, the existing studies are restricted to two *Aeromonas* species, *A. salmonicida* and *A. hydrophila*. Therefore, more studies are needed to optimize phage application under field conditions and to better understand the interactions between host fish, bacteria and phage.

The ability of phages to control *Aeromonas* species in aquaculture systems depends on several factors, such as phage selection, MOI, environmental factors that affect lytic phage viability (e.g., temperature, salinity, pH, UV radiation), administration routes and bacterial resistance to phages. In addition, the data obtained in in vitro assays cannot be directly applied to in vivo assays, nor can in vivo data for one phage be extrapolated to another phage. Before applying this approach commercially, phages must undergo efficacy testing to demonstrate their effectiveness and safety. Several factors need to be standardized and taken into account such as cost-effectiveness, administration method, the MOI that produces the best bacterial inactivation and stability of phage preparations. It is also necessary to explore the potential impact on the natural bacterial community and fish health, as a function of the type of bacteria and different environmental conditions, to allow its integration as a new antimicrobial processing technology in aquaculture.

Phage therapy is cost-effective, eco-friendly, safe for aquaculture species and end-users such as humans and animals. Despite the development of some bacterial degree of resistance towards phages, the harmful effects are negligible compared to the development of antibiotic resistance. The predisposition of bacteria to develop resistance to phages is ten

times slower than that of antibiotics and bacteria resistant to one phage can be infected by other phages with similar target ranges.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/antibiotics11020163/s1. Table S1: *Aeromonas* species typically associated with fish diseases and clinical signs; Table S2: In vitro studies of phage therapy for controlling *Aeromonas* sp. in fish; Table S3: In vivo studies of phage therapy for controlling *Aeromonas* sp. in fish. References [307–394] are cited in the supplementary materials.

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References

1. FAO. *The State of World Fisheries and Aquaculture 2020. Sustainability in Action*; FAO: Rome, Italy, 2020.
2. Almeida, A.; Cunha, Â.; Gomes, N.; Alves, E.; Costa, L.; Faustino, M. Phage therapy and photodynamic therapy: Low environmental impact approaches to inactivate microorganisms in fish farming plants. *Mar. Drugs* **2009**, *7*, 268–313. [CrossRef] [PubMed]
3. Castillo, D.; Higuera, G.; Villa, M.; Middelboe, M.; Dalsgaard, I.; Madsen, L.; Espejo, R.T. Diversity of *Flavobacterium psychrophilum* and the potential use of its phages for protection against bacterial cold water disease in salmonids. *J. Fish. Dis.* **2012**, *35*, 193–201. [CrossRef]
4. Christiansen, R.H.; Dalsgaard, I.; Middelboe, M.; Lauritsen, A.H.; Madsen, L. Detection and quantification of *Flavobacterium psychrophilum*-specific bacteriophages in vivo in rainbow trout upon oral administration: Implications for disease control in aquaculture. *Appl. Environ. Microbiol.* **2014**, *80*, 7683–7693. [CrossRef] [PubMed]
5. Dallaire-Dufresne, S.; Tanaka, K.H.; Trudel, M.V.; Lafaille, A.; Charette, S.J. Virulence, genomic features, and plasticity of *Aeromonas salmonicida* subsp. *salmonicida*, the causative agent of fish furunculosis. *Vet. Microbiol.* **2014**, *169*, 1–7. [CrossRef]
6. Sudheesh, P.S.; Al-Ghabshi, A.; Al-Mazrooei, N.; Al-Habsi, S. Comparative pathogenomics of bacteria causing infectious diseases in fish. *Int. J. Evol. Biol.* **2012**, *2012*, 457264. [CrossRef] [PubMed]
7. Sahoo, P.; Paul, A.; Sahoo, M.; Pattanayak, S.; Kumar, R.P.; Das, B. Incidences of infectious diseases in freshwater aquaculture farms of eastern India: A passive surveillance based study from 2014–2018. *J. Aquac. Res. Dev.* **2020**, *11*, 579.
8. Muniesa, A.; Basurco, B.; Aguilera, C.; Furones, D.; Reverté, C.; Sanjuan-Vilaplana, A.; Jansen, M.D.; Brun, E.; Tavornpanich, S. Mapping the knowledge of the main diseases affecting sea bass and sea bream in Mediterranean. *Transbound. Emerg. Dis.* **2020**, *67*, 1089–1100. [CrossRef]
9. Beaz-Hidalgo, R.; Figueras, M.J. *Aeromonas* spp. whole genomes and virulence factors implicated in fish disease. *J. Fish. Dis.* **2013**, *36*, 371–388. [CrossRef]
10. Chenia, H.Y. Prevalence and characterization of plasmid-mediated quinolone resistance genes in *Aeromonas* spp. isolated from South African freshwater fish. *Int. J. Food Microbiol.* **2016**, *231*, 26–32. [CrossRef]
11. Yu, J.; Koo, B.H.; Kim, D.H.; Kim, D.W.; Park, S.W. *Aeromonas sobria* infection in farmed mud loach (*Misgurnus mizolepis*) in Korea, a bacteriological survey. *Iran. J. Vet. Res.* **2015**, *16*, 194–201.
12. Austin, B.; Austin, D. Aeromonadaceae representative (*Aeromonas salmonicida*). In *Bacterial Fish Pathogens*; Springer: Dordrecht, The Netherlands, 2012; pp. 147–228.
13. Li, F.; Wu, D.; Gu, H.R.; Yin, M.; Ge, H.L.; Liu, X.H.; Huang, J.; Zhang, Y.G.; Wang, Z.J. *Aeromonas hydrophila* and *Aeromonas veronii* cause motile *Aeromonas* septicaemia in the cultured Chinese sucker, *Myxocyprinus asiaticus*. *Aquac. Res.* **2019**, *50*, 1515–1526. [CrossRef]

14. Dong, H.T.; Techatanakitarnan, C.; Jindakittikul, P.; Thaiprayoon, A.; Taengphu, S.; Charoensapsri, W.; Khunrae, P.; Rattanarojpong, T.; Senapin, S. *Aeromonas jandaei* and *Aeromonas veronii* caused disease and mortality in Nile tilapia, *Oreochromis niloticus* (L.). *J. Fish. Dis.* **2017**, *40*, 1395–1403. [CrossRef] [PubMed]
15. Coscelli, G.A.; Casabonne, C.; Morón-Alcain, E.; Arancegui, N.; Vigliano, F.A. *Aeromonas sobria*, an outbreak of natural infection in cultured silver catfish *Rhamdia quelen* (Quoy & Gaimard, 1824) in Argentina. *J. Fish. Dis.* **2017**, *40*, 1929–1933. [PubMed]
16. Nayak, S.K. Current prospects and challenges in fish vaccine development in India with special reference to *Aeromonas hydrophila* vaccine. *Fish. Shellfish Immunol.* **2020**, *100*, 283–299. [CrossRef] [PubMed]
17. Sommerset, I.; Krossøy, B.; Biering, E.; Frost, P. Vaccines for fish in aquaculture. *Expert Rev. Vaccines* **2005**, *4*, 89–101. [CrossRef] [PubMed]
18. Park, S. Disease control in korean aquaculture. *Fish. Pathol.* **2009**, *44*, 19–23. [CrossRef]
19. Håstein, T.; Gudding, R.; Evensen, O. Bacterial vaccines for fish-An update of the current situation worldwide. *Dev. Biol.* **2005**, *121*, 55–74.
20. Ma, J.; Bruce, T.J.; Jones, E.M.; Cain, K.D. A review of fish vaccine development strategies: Conventional methods and modern biotechnological approaches. *Microorganisms* **2019**, *7*, 569. [CrossRef]
21. Press, C.M.; Lillehaug, A. Vaccination in European salmonid aquaculture: A review of practices and prospects. *Br. Vet. J.* **1995**, *151*, 45–69. [CrossRef]
22. Vadstein, O. The use of immunostimulation in marine larviculture: Possibilities and challenges. *Aquaculture* **1997**, *155*, 401–417. [CrossRef]
23. Muktar, Y.; Tesfaye, S. Present status and future prospects of fish vaccination: A review. *J. Vet. Sci. Technol.* **2016**, *7*, 1–7. [CrossRef]
24. Pridgeon, J.; Klesius, P. Major bacterial diseases in aquaculture and their vaccine development. *CAB Rev. Perspect. Agric. Vet. Sci. Nutr. Nat. Resour.* **2012**, *7*, 1–16. [CrossRef]
25. Preena, P.G.; Swaminathan, T.R.; Kumar, V.J.R.; Singh, I.S.B. Antimicrobial resistance in aquaculture: A crisis for concern. *Biologia* **2020**, *75*, 1497–1517. [CrossRef]
26. Baquero, F.; Martínez, J.L.; Cantón, R. Antibiotics and antibiotic resistance in water environments. *Curr. Opin. Biotechnol.* **2008**, *19*, 260–265. [CrossRef] [PubMed]
27. Muziasari, W.I.; Pärnänen, K.; Johnson, T.A.; Lyra, C.; Karkman, A.; Stedtfeld, R.D.; Tamminen, M.; Tiedje, J.M.; Virta, M. Aquaculture changes the profile of antibiotic resistance and mobile genetic element associated genes in Baltic sea sediments. *FEMS Microbiol. Ecol.* **2016**, *92*, fiw052. [CrossRef]
28. Watts, J.E.M.; Schreier, H.J.; Lanska, L.; Hale, M.S. The rising tide of antimicrobial resistance in aquaculture: Sources, sinks and solutions. *Mar. Drugs* **2017**, *15*, 158. [CrossRef]
29. Santos, L.; Ramos, F. Antimicrobial resistance in aquaculture: Current knowledge and alternatives to tackle the problem. *Int. J. Antimicrob. Agents* **2018**, *52*, 135–143. [CrossRef]
30. Reith, M.E.; Singh, R.K.; Curtis, B.; Boyd, J.M.; Bouevitch, A.; Kimball, J.; Munholland, J.; Murphy, C.; Sarty, D.; Williams, J.; et al. The genome of *Aeromonas salmonicida* subsp. *salmonicida* A449: Insights into the evolution of a fish pathogen. *BMC Genom.* **2008**, *9*, 427.
31. Kim, J.H.; Hwang, S.Y.; Son, J.S.; Han, J.E.; Jun, J.W.; Shin, S.P.; Choresca, C.; Choi, Y.J.; Park, Y.H.; Park, S.C. Molecular characterization of tetracycline- and quinolone-resistant *Aeromonas salmonicida* isolated in Korea. *J. Vet. Sci.* **2011**, *12*, 41–47. [CrossRef]
32. Pereira, C.; Costa, P.; Duarte, J.; Balcão, V.M.; Almeida, A. Phage therapy as a potential approach in the biocontrol of pathogenic bacteria associated with shellfish consumption. *Int. J. Food Microbiol.* **2021**, *338*, 108995. [CrossRef]
33. Caflisch, K.; Suh, G.; Patel, R. Biological challenges of phage therapy and proposed solutions: A literature review. *Expert Rev. Anti. Infect. Ther.* **2019**, *17*, 1011–1041. [CrossRef] [PubMed]
34. Moye, Z.D.; Woolston, J.; Sulakvelidze, A. Bacteriophage applications for food production and processing. *Viruses* **2018**, *10*, 205. [CrossRef] [PubMed]
35. Svircev, A.; Roach, D.; Castle, A. Framing the future with bacteriophages in agriculture. *Viruses* **2018**, *10*, 218. [CrossRef] [PubMed]
36. Carvalho, C.M.; Santos, S.B.; Kropinski, A.M.; Ferreira, E.C.; Azeredo, J. Phages as therapeutic tools to control major foodborne pathogens: *Campylobacter* and *Salmonella*. In *Bacteriophages*; Kurtböke, I., Ed.; InTech: Rijeka, Croatia, 2011; pp. 179–214.
37. Endersen, L.; O'Mahony, J.; Hill, C.; Ross, R.P.; McAuliffe, O.; Coffey, A. Phage therapy in the food industry. *Annu. Rev. Food Sci. Technol.* **2014**, *5*, 327–349. [CrossRef]
38. Choudhury, T.; Nagaraju, V.; Gita, S.; Paria, A.; Parhi, J. Advances in bacteriophage research for bacterial disease control in aquaculture. *Rev. Fish. Sci. Aquac.* **2017**, *25*, 113–125. [CrossRef]
39. Culot, A.; Grosset, N.; Gautier, M. Overcoming the challenges of phage therapy for industrial aquaculture: A review. *Aquaculture* **2019**, *513*, 734423. [CrossRef]
40. Oliveira, J.; Castilho, F.; Cunha, A.; Pereira, M.J. Bacteriophage therapy as a bacterial control strategy in aquaculture. *Aquac. Int.* **2012**, *20*, 879–910. [CrossRef]
41. Ramasamy, P. Phage therapy for control of bacterial diseases. In *Crustacea*; Diarte-Plata, G., Escamilla-Montes, R., Eds.; InTech: London, UK, 2019; pp. 1–31.
42. Abedon, S.T.; Kuhl, S.J.; Blasdel, B.G.; Kutter, E.M. Phage treatment of human infections. *Bacteriophage* **2011**, *1*, 66–85. [CrossRef]

43. Kutter, E.; De Vos, D.; Gvasalia, G.; Alavidze, Z.; Gogokhia, L.; Kuhl, S.; Abedon, S.T. Phage therapy in clinical practice: Treatment of human infections. *Curr. Pharm. Biotechnol.* **2010**, *11*, 69–86. [CrossRef]
44. Furfaro, L.L.; Payne, M.S.; Chang, B.J. Bacteriophage therapy: Clinical trials and regulatory hurdles. *Front. Cell. Infect. Microbiol.* **2018**, *8*, 376. [CrossRef]
45. Borie, C.; Robeson, J.; Galarce, N. Lytic bacteriophages in veterinary medicine: A therapeutic option against bacterial pathogens? *Arch. Med. Vet.* **2014**, *46*, 167–179. [CrossRef]
46. Gigante, A.; Atterbury, R.J. Veterinary use of bacteriophage therapy in intensively-reared livestock. *Virol. J.* **2019**, *16*, 155. [CrossRef] [PubMed]
47. Squires, R. Bacteriophage therapy for management of bacterial infections in veterinary practice: What was once old is new again. *N. Z. Vet. J.* **2011**, *66*, 229–235. [CrossRef] [PubMed]
48. Wernicki, A.; Nowaczek, A.; Urban-Chmiel, R. Bacteriophage therapy to combat bacterial infections in poultry. *Virol. J.* **2017**, *14*, 179. [CrossRef]
49. Fernández, L.; Gutiérrez, D.; Rodríguez, A.; García, P. Application of bacteriophages in the agro-food sector: A long way toward approval. *Front. Cell. Infect. Microbiol.* **2018**, *8*, 296. [CrossRef]
50. Arkadiusz Wojtasik, A.; Górecka, E.; Wójcik, E.; Stańczyk, M.; Kołsut, J.; Klimczak, J.; Dastych, J.; Siwicki, A.; Schulz, P. Bacteriophage Strains and Their Applications. 2017. Available online: https://patents.google.com/patent/PL416716A1/pl (accessed on 3 November 2021).
51. Silva, Y.; Moreirinha, C.; Pereira, C.; Costa, L.; Rocha, R.J.M.; Cunha, Â.; Gomes, N.C.M.; Calado, R.; Almeida, A. Biological control of *Aeromonas salmonicida* infection in juvenile Senegalese sole (*Solea senegalensis*) with phage AS-A. *Aquaculture* **2016**, *450*, 225–233. [CrossRef]
52. Silva, Y.; Costa, L.; Pereira, C.; Mateus, C.; Cunha, Â.; Calado, R.; Gomes, N.; Pardo, M.; Hernandez, I.; Almeida, A. Phage therapy as an approach to prevent *Vibrio anguillarum* infections in fish larvae production. *PLoS ONE* **2014**, *9*, e114197. [CrossRef]
53. Fernández-Bravo, A.; Figueras, M.J. An update on the genus *Aeromonas*: Taxonomy, epidemiology, and pathogenicity. *Microorganisms* **2020**, *8*, 129. [CrossRef]
54. Pessoa, R.; de Oliveira, W.; Marques, D.; Correia, M.; de Carvalho, E.; Coelho, L. The genus *Aeromonas*: A general approach. *Microb. Pathog.* **2019**, *130*, 81–94. [CrossRef]
55. Park, S.Y.; Han, J.E.; Kwon, H.; Park, S.C.; Kim, J.H. Recent insights into *Aeromonas salmonicida* and its bacteriophages in aquaculture: A comprehensive review. *J. Microbiol. Biotechnol.* **2020**, *30*, 1443–1457. [CrossRef]
56. Zhou, H.; Gai, C.; Ye, G.; An, J.; Liu, K.; Xu, L.; Cao, H. *Aeromonas hydrophila*, an emerging causative agent of freshwater-farmed whiteleg shrimp *Litopenaeus vannamei*. *Microorganisms* **2019**, *7*, 450. [CrossRef] [PubMed]
57. Rasmussen-Ivey, C.R.; Hossain, M.J.; Odom, S.E.; Terhune, J.S.; Hemstreet, W.G.; Shoemaker, C.A.; Zhang, D.; Xu, D.H.; Griffin, M.J.; Liu, Y.J.; et al. Classification of a hypervirulent *Aeromonas hydrophila* pathotype responsible for epidemic outbreaks in warm-water fishes. *Front. Microbiol.* **2016**, *7*, 1615. [CrossRef] [PubMed]
58. Igbinosa, I.H.; Igbinosa, E.O.; Okoh, A.I. Detection of antibiotic resistance, virulence gene determinants and biofilm formation in *Aeromonas* species isolated from cattle. *Environ. Sci. Pollut. Res.* **2015**, *22*, 17596–17605. [CrossRef] [PubMed]
59. Chen, P.L.; Lamy, B.; Ko, W.C. *Aeromonas dhakensis*, an increasingly recognized human pathogen. *Front. Microbiol.* **2016**, *7*, 793. [CrossRef]
60. Orozova, P.; Chikova, V.; Najdenski, H. Antibiotic resistance of pathogenic for fish isolates of *Aeromonas* spp. *Bulg. J. Agric. Sci.* **2010**, *16*, 376–386.
61. Stratev, D.; Daskalov, H.; Vashin, I. Characterisation and determination of antimicrobial resistance of β-haemolytic *Aeromonas* spp. isolated from common carp (*Cyprinus carpio* L.). *Rev. Med. Vet. (Toulouse)* **2015**, *166*, 54–61.
62. Mulyani, Y.; Aryantha, I.N.P.; Suhandono, S.; Pancoro, A. Intestinal bacteria of common carp (*Cyprinus carpio* L.) as a biological control agent for *Aeromonas*. *J. Pure Appl. Microbiol.* **2018**, *12*, 601–610. [CrossRef]
63. Hossain, M.J.; Sun, D.; McGarey, D.J.; Wrenn, S.; Alexander, L.M.; Martino, M.E.; Xing, Y.; Terhune, J.S.; Liles, M.R. An asian origin of virulent *Aeromonas hydrophila* responsible for disease epidemics in united states-farmed catfish. *MBio* **2014**, *5*, e00848-14. [CrossRef]
64. Pablos, M.; Rodríguez-Calleja, J.M.; Santos, J.A.; Otero, A.; García-López, M.L. Occurrence of motile *Aeromonas* in municipal drinking water and distribution of genes encoding virulence factors. *Int. J. Food Microbiol.* **2009**, *135*, 158–164. [CrossRef]
65. Hoel, S.; Vadstein, O.; Jakobsen, A.N. Species distribution and prevalence of putative virulence factors in mesophilic *Aeromonas* spp. isolated from fresh retail sushi. *Front. Microbiol.* **2017**, *8*, 931. [CrossRef]
66. Igbinosa, I.H.; Beshiru, A.; Odjadjare, E.E.; Ateba, C.N.; Igbinosa, E.O. Pathogenic potentials of *Aeromonas* species isolated from aquaculture and abattoir environments. *Microb. Pathog.* **2017**, *107*, 185–192. [CrossRef] [PubMed]
67. Yu, J.H.; Han, J.J.; Kim, H.J.; Kang, S.G.; Park, S.W. First report of *Aeromonas veronii* infection in farmed Israeli carp *Cyprinus carpio* in Korea. *J. Fish Pathol.* **2010**, *23*, 165–176.
68. Hu, M.; Wang, N.; Pan, Z.H.; Lu, C.P.; Liu, Y.J. Identity and virulence properties of *Aeromonas* isolates from diseased fish, healthy controls and water environment in China. *Lett. Appl. Microbiol.* **2012**, *55*, 224–233. [CrossRef] [PubMed]
69. Rashid, M.M.; Hossain, M.; Ali, M. Isolation and identification of *Aeromonas hydrophila* from silver carp and its culture environment from Mymensingh region. *J. Bangladesh Agric. Univ.* **2013**, *11*, 373–376. [CrossRef]

70. Yan, Y.; Liu, Y.; Mo, Z.; Li, J.; Liu, S.; Gao, Y.; Li, G. Development of *Aeromonas salmonicida* subsp. *masoucida* vaccine in turbot and evaluation of protection efficacy under field conditions. *Aquaculture* **2021**, *544*, 737035.
71. Lin, Q.; Li, J.; Fu, X.; Liu, L.; Liang, H.; Niu, Y.; Huang, C.; Huang, Z.; Mo, Z.; Li, N. Hemorrhagic gill disease of chinese perch caused by *Aeromonas salmonicida* subsp. *salmonicida in China*. *Aquaculture* **2020**, *519*, 734775. [CrossRef]
72. Coscelli, G.A.; Bermúdez, R.; Losada, A.P.; Faílde, L.D.; Santos, Y.; Quiroga, M.I. Acute *Aeromonas salmonicida* infection in turbot (*Scophthalmus maximus* L.). Histopathological and immunohistochemical studies. *Aquaculture* **2014**, *430*, 79–85. [CrossRef]
73. Bjarnheidur, K.; Bryndis, B. *Aeromonas salmonicida* and *A. hydrophila*. In *Fish Viruses and Bacteria: Pathobiology and Protection*; Woo, P., Cipriano, R., Eds.; CABI: Oxfordshire, UK, 2017; pp. 173–189.
74. Tewari, R.; Dudeja, M.; Nandy, S.; Das, A.K. Isolation of *Aeromonas salmonicida* from human blood sample: A case report. *J. Clin. Diagnostic Res.* **2014**, *8*, 139–140. [CrossRef]
75. Salehi, M.R.; Shadvar, S.; Sadeghian, M.; Doomanlou, M.; Abdollahi, A.; Manshadi, S.A.D.; Sardari, A.; Rahdar, H.A.; Feizabadi, M.M. Endocarditis with *Aeromonas salmonicida*. *IDCases* **2019**, *18*, e00625. [CrossRef]
76. Vincent, A.T.; Fernández-Bravo, A.; Sanchis, M.; Mayayo, E.; Figueras, M.J.; Charette, S.J. Investigation of the virulence and genomics of *Aeromonas salmonicida* strains isolated from human patients. *Infect. Genet. Evol.* **2019**, *68*, 1–9. [CrossRef]
77. Martínez-Murcia, A.; Beaz-Hidalgo, R.; Navarro, A.; Carvalho, M.J.; Aravena-Román, M.; Correia, A.; Figueras, M.J.; Saavedra, M.J. *Aeromonas lusitana* sp. nov., isolated from untreated water and vegetables. *Curr. Microbiol.* **2016**, *72*, 795–803. [CrossRef]
78. Santos, Y.; Toranzo, A.; Dopazo, C.; Nieto, T.; Barja, J. Relationships among virulence for fish, enterotoxigenicity, and phenotypic characteristics of motile *Aeromonas*. *Aquaculture* **1987**, *67*, 29–39. [CrossRef]
79. Palumbo, S.A.; Maxino, F.; Williams, A.C. Starch-ampicillin agar for the quantitative detection of *Aeromonas hydrophila*. *Appl. Environ. Microbiol.* **1985**, *50*, 1027–1030. [CrossRef] [PubMed]
80. Dallal, M.; Fard, R.; Talkhabi, M.; Aghaiyan, L.; Salehipour, Z. Prevalence, virulence and antimicrobial resistance patterns of *Aeromonas* spp. isolated from children with diarrhea. *Germs* **2016**, *6*, 91–96. [CrossRef] [PubMed]
81. Albert, M.J.; Ansaruzzaman, M.; Talukder, K.A.; Chopra, A.K.; Kuhn, I.; Rahman, M.; Faruque, A.S.G.; Islam, M.S.; Sack, R.B.; Mollby, R. Prevalence of enterotoxin genes in *Aeromonas* spp. isolated from children with diarrhea, healthy controls, and the environment. *J. Clin. Microbiol.* **2000**, *38*, 3785–3790. [CrossRef] [PubMed]
82. Latif-Eugenín, F.; Beaz-Hidalgo, R.; Figueras, M. First record of the rare species *Aeromonas schubertii* from mussels: Phenotypic and genetic reevaluation of the species and a review of the literature. *Arch. Microbiol* **2016**, *198*, 333–345. [CrossRef]
83. Parker, J.L.; Shaw, J.G. *Aeromonas* spp. clinical microbiology and disease. *J. Infect.* **2011**, *62*, 109–118. [CrossRef]
84. John, N.; Vidyalakshmi, V.; Hatha, A. Effect of pH and salinity on the production of extracellular virulence factors by *Aeromonas* from food sources. *J. Food Sci.* **2019**, *84*, 2250–2255. [CrossRef]
85. Hossain, S.; De Silva, B.C.J.; Dahanayake, P.S.; De Zoysa, M.; Heo, G. Phylogenetic characteristics, virulence properties and antibiogram profile of motile *Aeromonas* spp. isolated from ornamental guppy (*Poecilia reticulata*). *Arch. Microbiol.* **2020**, *202*, 501–509. [CrossRef]
86. Schwenteit, J.; Gram, L.; Nielsen, K.F.; Fridjonsson, O.H.; Bornscheuer, U.T.; Givskov, M.; Gudmundsdottir, B.K. Quorum sensing in *Aeromonas salmonicida* subsp. *achromogenes* and the effect of the autoinducer synthase AsaI on bacterial virulence. *Vet. Microbiol.* **2011**, *147*, 389–397.
87. da Silva, B.C.; Mouriño, J.L.P.; Vieira, F.N.; Jatobá, A.; Seiffert, W.Q.; Martins, M.L. Haemorrhagic septicaemia in the hybrid surubim (*Pseudoplatystoma corruscans* × *Pseudoplatystoma fasciatum*) caused by *Aeromonas hydrophila*. *Aquac. Res.* **2012**, *43*, 908–916. [CrossRef]
88. Nielsen, M.E.; Høi, L.; Schmidt, A.S.; Qian, D.; Shimada, T.; Shen, J.Y.; Larsen, J.L. Is *Aeromonas hydrophila* the dominant motile Aeromonas species that causes disease outbreaks in aquaculture production in the Zhejiang Province of China? *Dis. Aquat. Organ.* **2001**, *46*, 23–29. [CrossRef] [PubMed]
89. Peterman, M.A.; Posadas, B.C. Direct economic impact of fish diseases on the East Mississippi catfish industry. *N. Am. J. Aquac.* **2019**, *81*, 222–229. [CrossRef]
90. Pang, M.; Jiang, J.; Xie, X.; Wu, Y.; Dong, Y.; Kwok, A.H.Y.; Zhang, W.; Yao, H.; Lu, C.; Leung, F.C.; et al. Novel insights into the pathogenicity of epidemic *Aeromonas hydrophila* ST251 clones from comparative genomics. *Sci. Rep.* **2015**, *5*, 9833. [CrossRef]
91. Cao, Y.; Li, S.; Han, S.; Wang, D.; Zhao, J.; Xu, L.; Liu, H.; Lu, T. Characterization and application of a novel *Aeromonas* bacteriophage as treatment for pathogenic *Aeromonas hydrophila* infection in rainbow trout. *Aquaculture* **2020**, *523*, 735193. [CrossRef]
92. Hassan, S.W.M.; Ali, S.M.; AlMisherfi, M.M. Isolation and molecular characterization of some marine Aeromonas phages: Protective effects for Nile tilapia infected with *Aeromonas hydrophila*. *J. Pure Appl. Microbiol.* **2018**, *12*, 1175–1185. [CrossRef]
93. El-Araby, D.; Gamal, E.-D.; Marihan, M.T. New approach to use phage therapy against *Aeromonas hydrophila* induced motile *Aeromonas* septicemia in Nile tilapia. *Mar. Sci. Res. Dev.* **2016**, *6*, 6–11.
94. Dien, L.T.; Ky, L.B.; Huy, B.T.; Mursalim, M.F.; Kayansamruaj, P.; Senapin, S.; Rodkhum, C.; Dong, H. Characterization and protective effects of lytic bacteriophage pAh6. 2TG against a pathogenic multidrug-resistant *Aeromonas hydrophila* in Nile tilapia (*Oreochromis niloticus*). *Transbound. Emerg. Dis.* **2021**, 1–16.
95. Le, T.S.; Nguyen, T.H.; Vo, H.P.; Doan, V.C.; Nguyen, H.L.; Tran, M.T.; Tran, T.T.; Southgate, P.C.; İpek Kurtböke, D. Protective effects of bacteriophages against *Aeromonas hydrophila* species causing Motile *Aeromonas* Septicemia (MAS) in striped catfish. *Antibiotics* **2018**, *7*, 16. [CrossRef]

96. Biradar, S.; Goud, N.; Neogi, U.; Saumya, R. In vitro and in vivo antibacterial studies of medicinal plant on motile Aeromonad septicemia in fish caused by *Aeromonas hydrophila*. *J. Fish. Aquat. Sci.* **2007**, *2*, 417–421. [CrossRef]
97. Gupta, A.; Gupta, S.K.; Priyam, M.; Siddik, M.A.B.; Kumar, N.; Mishra, P.K.; Gupta, K.K.; Sarkar, B.; Sharma, T.R.; Pattanayak, A. Immunomodulation by dietary supplements: A preventive health strategy for sustainable aquaculture of tropical freshwater fish, *Labeo rohita* (Hamilton, 1822). *Rev. Aquac.* **2021**, *13*, 2364–2394. [CrossRef]
98. Bebak, J.; Wagner, B.; Burnes, B.; Hanson, T. Farm size, seining practices, and salt use: Risk factors for *Aeromonas hydrophila* outbreaks in farm-raised catfish, Alabama, USA. *Prev. Vet. Med.* **2015**, *118*, 161–168. [CrossRef] [PubMed]
99. Zhang, D.; Xu, D.-H.; Shoemaker, C.A.; Beck, B.H. The severity of motile *Aeromonas* septicemia caused by virulent *Aeromonas hydrophila* in channel catfish is influenced by nutrients and microbes in water. *Aquaculture* **2020**, *519*, 734898. [CrossRef]
100. Roquigny, R.; Mougin, J.; Le Bris, C.; Bonnin-Jusserand, M.; Doyen, P.; Grard, T. Characterization of the marine aquaculture microbiome: A seasonal survey in a seabass farm. *Aquaculture* **2021**, *531*, 735987. [CrossRef]
101. Sahoo, P.K.; Swaminathan, T.R.; Abraham, T.J.; Kumar, R.; Pattanayak, S.; Mohapatra, A.; Rath, S.S.; Patra, A.; Adikesavalu, H.; Sood, N.; et al. Detection of goldfish haematopoietic necrosis herpes virus (Cyprinid herpesvirus-2) with multi-drug resistant *Aeromonas hydrophila* infection in goldfish: First evidence of any viral disease outbreak in ornamental freshwater aquaculture farms in India. *Acta Trop.* **2016**, *161*, 8–17. [CrossRef] [PubMed]
102. Sicuro, B.; Pastorino, P.; Barbero, R.; Barisone, S.; Dellerba, D.; Menconi, V.; Righetti, M.; De Vita, V.; Prearo, M. Prevalence and antibiotic sensitivity of bacteria isolated from imported ornamental fish in Italy: A translocation of resistant strains? *Prev. Vet. Med.* **2020**, *175*, 104880. [CrossRef] [PubMed]
103. Eissa, A.E.; Attia, M.M.; Elgendy, M.Y.; Ismail, G.A.; Sabry, N.M.; Prince, A.; Mahmoud, M.A.; El-Demerdash, G.O.; Abdelsalam, M.; Derwa, H.I.M. *Streptococcus*, *Centrocestus formosanus* and *Myxobolus tilapiae* concurrent infections in farmed Nile tilapia (*Oreochromis niloticus*). *Microb. Pathog.* **2021**, *158*, 105084. [CrossRef]
104. van den Berg, A.H.; McLaggan, D.; Diéguez-Uribeondo, J.; van West, P. The impact of the water moulds *Saprolegnia diclina* and *Saprolegnia parasitica* on natural ecosystems and the aquaculture industry. *Fungal Biol. Rev.* **2013**, *27*, 33–42. [CrossRef]
105. Huang, X.; Xiong, G.; Feng, Y.; Wang, K.; Liu, Y.; Zhong, L.; Liu, S.; Geng, Y.; Ouyang, P.; Chen, D.; et al. Ulcerative disease emergence in grass carp (*Ctenopharyngodon idellus*) aquaculture in China: Possible impact of temperature abnormality. *Aquaculture* **2020**, *517*, 734811. [CrossRef]
106. Kousar, R.; Shafi, N.; Andleeb, S.; Ali, N.M.; Akhtar, T.; Khalid, S. Assessment and incidence of fish associated bacterial pathogens at hatcheries of Azad Kashmir, Pakistan. *Br. J. Biol.* **2020**, *80*, 607–614. [CrossRef]
107. Jia, B.; Delphino, M.K.V.C.; Awosile, B.; Hewison, T.; Whittaker, P.; Morrison, D.; Kamaitis, M.; Siah, A.; Milligan, B.; Johnson, S.C.; et al. Review of infectious agent occurrence in wild salmonids in British Columbia, Canada. *J. Fish. Dis.* **2020**, *43*, 153–175. [CrossRef] [PubMed]
108. Lulijwa, R.; Rupia, E.J.; Alfaro, A.C. Antibiotic use in aquaculture, policies and regulation, health and environmental risks: A review of the top 15 major producers. *Rev. Aquac.* **2020**, *12*, 640–663. [CrossRef]
109. Cabello, F.C.; Godfrey, H.P.; Tomova, A.; Ivanova, L.; Dölz, H.; Millanao, A.; Buschmann, A.H. Antimicrobial use in aquaculture re-examined: Its relevance to antimicrobial resistance and to animal and human health. *Environ. Microbiol.* **2013**, *15*, 1917–1942. [CrossRef] [PubMed]
110. Liu, X.; Steele, J.C.; Meng, X.Z. Usage, residue, and human health risk of antibiotics in Chinese aquaculture: A review. *Environ. Pollut.* **2017**, *223*, 161–169. [CrossRef] [PubMed]
111. Adams, A.; Aoki, T.; Berthe, F.; Grisez, L.; Karunasagar, I. Recent technological advancements on aquatic animal health and their contributions toward reducing disease risks-A review. In *Diseases in Asian Aquaculture VI*; Bondad-Reantaso, M., Mohan, C., Crumlish, M., Subasinghe, R., Eds.; Fish Health Section, Asian Fisheries Society: Manile, PI, USA, 2008; p. 505.
112. Chuah, L.O.; Effarizah, M.E.; Goni, A.M.; Rusul, G. Antibiotic application and emergence of multiple antibiotic resistance (MAR) in global catfish aquaculture. *Curr. Environ. Heal. Rep.* **2016**, *3*, 118–127. [CrossRef]
113. Sun, R.; Chen, J.; Pan, C.; Sun, Y.; Mai, B.; Li, Q.X. Antibiotics and food safety in aquaculture. *J. Agric. Food Chem.* **2020**, *68*, 11908–11919.
114. Lillehaug, A.; Lunestad, B.T.; Grave, K. Epidemiology of bacterial diseases in Norwegian aquaculture—A description based on antibiotic prescription data for the ten-year period 1991 to 2000. *Dis. Aquat. Organ.* **2003**, *53*, 115–125. [CrossRef]
115. Burridge, L.; Weis, J.S.; Cabello, F.; Pizarro, J.; Bostick, K. Chemical use in salmon aquaculture: A review of current practices and possible environmental effects. *Aquaculture* **2010**, *306*, 7–23. [CrossRef]
116. Evensen, Ø. Development of fish vaccines: Focusing on methods. In *Fish Vaccines, Birkhäuser Advances in Infectious Diseases*; Adams, A., Ed.; Springer: Basel, Switzerland, 2016; pp. 53–74.
117. Song, C.; Zhang, C.; Fan, L.; Qiu, L.; Wu, W.; Meng, S.; Hu, G.; Kamira, B.; Chen, J. Occurrence of antibiotics and their impacts to primary productivity in fishponds around Tai Lake, China. *Chemosphere* **2016**, *161*, 127–135. [CrossRef]
118. Rico, A.; Phu, T.M.; Satapornvanit, K.; Min, J.; Shahabuddin, A.M.; Henriksson, P.J.G.; Murray, F.J.; Little, D.C.; Dalsgaard, A.; Van den Brink, P.J. Use of veterinary medicines, feed additives and probiotics in four major internationally traded aquaculture species farmed in Asia. *Aquaculture* **2013**, *412–413*, 231–243. [CrossRef]
119. Martin, M.J.; Thottathil, S.E.; Newman, T.B. Antibiotics overuse in animal agriculture: A call to action for health care providers. *Am. J. Public Health* **2015**, *105*, 2409–2410. [CrossRef] [PubMed]

120. Hossain, A.; Nakamichi, S.; Habibullah-Al-Mamun, M.; Tani, K.; Masunaga, S.; Matsuda, H. Occurrence, distribution, ecological and resistance risks of antibiotics in surface water of finfish and shellfish aquaculture in Bangladesh. *Chemosphere* **2017**, *188*, 329–336. [CrossRef] [PubMed]
121. Ali, S.; Akhter, S.; Muhammad, A.; Khan, I.; Khan, W.A.; Iqbal, M.N.; Umar, S.; Ahmed, H.; Ali, Q. Identification, characterization and antibiotic sensitivity of *Aeromonas hydrophila*, a causative agent of epizootic ulcerative syndrome in wild and farmed fish from potohar, Pakistan. *Pak. J. Zool.* **2016**, *48*, 899–901.
122. Ashiru, A.; Uaboi-Egbeni, P.; Oguntowo, J.; Idika, C. Isolation and antibiotic profile of *Aeromonas* species from tilapia fish (*Tilapia nilotica*) and catfish (*Clarias betrachus*). *Pak. J. Nutr.* **2011**, *10*, 982–986. [CrossRef]
123. Odeyemi, O.A.; Ahmad, A. Antibiotic resistance profiling and phenotyping of *Aeromonas* species isolated from aquatic sources. *Saudi J. Biol. Sci.* **2017**, *24*, 65–70. [CrossRef]
124. Snieszko, S.; Bullock, G. Treatment of sulfonamide-resistant furunculosis in trout and determination of drug sensitivity. *Fish. Bull.* **1957**, *125*, 555–564.
125. Jacobs, L.; Chenia, H.Y. Characterization of integrons and tetracycline resistance determinants in *Aeromonas* spp. isolated from South African aquaculture systems. *Int. J. Food Microbiol.* **2007**, *114*, 295–306. [CrossRef]
126. Grave, K.; Markestad, A.; Bangen, M. Comparison in prescribing patterns of antibacterial drugs in salmonid farming in Norway during the periods 1980–1988 and 1989–1994. *J. Vet. Pharmacol. Ther.* **1996**, *19*, 184–191. [CrossRef]
127. Dobiasova, H.; Kutilova, I.; Piackova, V.; Vesely, T.; Cizek, A.; Dolejska, M. Ornamental fish as a source of plasmid-mediated quinolone resistance genes and antibiotic resistance plasmids. *Vet. Microbiol.* **2014**, *171*, 413–421. [CrossRef]
128. Han, J.; Kim, J.; Cheresca Jr, C.; Shin, S.; Jun, J.; Chai, J.; Han, S.; Park, S. First description of the qnrS -like (qnrS5) gene and analysis of quinolone resistance-determining regions in motile *Aeromonas* spp. from diseased fish and water. *Res. Microbiol.* **2012**, *163*, 73–79. [CrossRef]
129. Verner-jeffreys, D.W.; Welch, T.J.; Schwarz, T.; Pond, M.J.; Martin, J.; Haig, S.J.; Rimmer, G.S.E.; Roberts, E.; Morrison, V. High prevalence of multidrug-tolerant bacteria and associated antimicrobial resistance genes isolated from ornamental fish and their carriage water. *PLoS ONE* **2009**, *4*, e8388. [CrossRef] [PubMed]
130. Dadar, M.; Dhama, K.; Vakharia, V.N.; Hoseinifar, S.H.; Karthik, K.; Tiwari, R.; Khandia, R.; Munjal, A.; Salgado-Miranda, C.; Joshi, S.K. Advances in aquaculture vaccines against fish pathogens: Global status and current trends. *Rev. Fish. Sci. Aquac.* **2017**, *25*, 184–217. [CrossRef]
131. Ben Hamed, S.; Tapia-Paniagua, S.T.; Moriñigo, M.Á.; Ranzani-Paiva, M.J.T. Advances in vaccines developed for bacterial fish diseases, performance and limits. *Aquac. Res.* **2021**, *52*, 2377–2390. [CrossRef]
132. Duff, D. The oral immunization of trout against *Bacterium salmonicida*. *J. Immunol.* **1942**, *42*, 87–94.
133. Shoemaker, C.A.; Klesius, P.H.; Evans, J.J.; Arias, C.R. Use of modified live vaccines in aquaculture. *J. World Aquac. Soc.* **2009**, *40*, 573–585. [CrossRef]
134. Bricknell, I.R.; Bowden, T.J.; Lomax, J.; Ellis, A.E. Antibody response and protection of Atlantic salmon (*Salmo salar*) immunised with an extracellular polysaccharide of *Aeromonas salmonicida*. *Fish. Shellfish Immunol.* **1997**, *7*, 791–796. [CrossRef]
135. Adams, A. Progress, challenges and opportunities in fish vaccine development. *Fish. Shellfish Immunol.* **2019**, *90*, 210–214. [CrossRef]
136. Wang, Q. Current use and development of fi sh vaccines in China. *Fish. Shellfis* **2020**, *96*, 223–234. [CrossRef]
137. MDS Animal Health Aquavac® FNM. Available online: https://www.msd-animal-health-me.com/products/aquavac-fnm/ (accessed on 18 November 2021).
138. PHARMAQ Alpha Ject Panga 2. Available online: https://www.pharmaq.com/no/pharmaq/ (accessed on 18 November 2021).
139. Rao, Y.V.; Das, B.K.; Jyotyrmayee, P.; Chakrabarti, R. Effect of *Achyranthes aspera* on the immunity and survival of *Labeo rohita* infected with *Aeromonas hydrophila*. *Fish. Shellfish Immunol.* **2006**, *20*, 263–273.
140. Magnadottir, B. Immunological control of fish diseases. *Mar. Biotechnol.* **2010**, *12*, 361–379. [CrossRef]
141. Han, B.; Xu, K.; Liu, Z.; Ge, W.; Shao, S.; Li, P.; Yan, N.; Li, X. Oral yeast-based DNA vaccine confers effective protection from *Aeromonas hydrophila* infection on *Carassius auratus*. *Fish. Shellfish Immunol.* **2019**, *84*, 948–954. [CrossRef] [PubMed]
142. Liu, L.; Gong, Y.-X.; Liu, G.-L.; Zhu, B.; Wang, G.-X. Protective immunity of grass carp immunized with DNA vaccine against *Aeromonas hydrophila* by using carbon nanotubes as a carrier molecule. *Fish. Shellfish Immunol.* **2016**, *55*, 516–522. [CrossRef] [PubMed]
143. Mzula, A.; Wambura, P.N.; Mdegela, R.H.; Shirima, G.M. Phenotypic and molecular detection of Aeromonads infection in farmed Nile tilapia in southern Highland and northern Tanzania. *Heliyon* **2019**, *5*, e02220. [CrossRef] [PubMed]
144. Melingen, G.O.; Wergeland, H.I. Physiological effects of an oil-adjuvanted vaccine on out-of-season Atlantic salmon (*Salmo salar* L.) smolt. *Aquaculture* **2002**, *214*, 397–409. [CrossRef]
145. Koppang, E.O.; Haugarvoll, E.; Hordvik, I.; Aune, L.; Poppe, T.T. Vaccine-associated granulomatous inflammation and melanin accumulation in Atlantic salmon, *Salmo salar* L., white muscle. *J. Fish. Dis.* **2005**, *28*, 13–22. [CrossRef]
146. Berg, A.; Rødseth, O.M.; Hansen, T. Fish size at vaccination influence the development of side-effects in Atlantic salmon (*Salmo salar* L.). *Aquaculture* **2007**, *265*, 9–15. [CrossRef]
147. Coscelli, G.A.; Bermúdez, R.; Losada, A.P.; Santos, Y.; Quiroga, M.I. Vaccination against *Aeromonas salmonicida* in turbot (*Scophthalmus maximus* L.): Study of the efficacy, morphological changes and antigen distribution. *Aquaculture* **2015**, *445*, 22–32. [CrossRef]

148. Dang, T.H.O.; Xuan, T.T.T.; Duyen, L.T.M.; Le, N.P.; Hoang, H.A. Protective efficacy of phage PVN02 against haemorrhagic septicaemia in striped catfish *Pangasianodon hypophthalmus* via oral administration. *J. Fish. Dis.* **2021**, *44*, 1255–1263. [CrossRef]
149. Akmal, M.; Rahimi-Midani, A.; Hafeez-Ur-rehman, M.; Hussain, A.; Choi, T.J. Isolation, characterization, and application of a bacteriophage infecting the fish pathogen *Aeromonas hydrophila*. *Pathogens* **2020**, *9*, 215. [CrossRef]
150. Duarte, J.; Pereira, C.; Moreirinha, C.; Salvio, R.; Lopes, A.; Wang, D.; Almeida, A. New insights on phage efficacy to control *Aeromonas salmonicida* in aquaculture systems: An in vitro preliminary study. *Aquaculture* **2018**, *495*, 970–982. [CrossRef]
151. Ceyssens, P.; Lavigne, R. Introduction to bacteriophage biology and diversity. In *Baccteriophages in the Control of Food and Waterborne Pathogens*; Sabour, P.M., Griffiths, M.W., Eds.; ASM Press: Washington, DC, USA, 2010; pp. 11–29.
152. Skurnik, M.; Strauch, E. Phage therapy: Facts and fiction. *Int. J. Med. Microbiol.* **2006**, *296*, 5–14. [CrossRef] [PubMed]
153. Belay, M.; Sisay, T.; Wolde, T. Bacteriophages and phage products: Applications in medicine and biotechnological industries, and general concerns. *Sci. Res. Essays* **2018**, *13*, 55–70.
154. Harada, L.K.; Silva, E.C.; Campos, W.F.; Del Fiol, F.S.; Vila, M.; Dąbrowska, K.; Krylov, V.N.; Balcão, V.M. Biotechnological applications of bacteriophages: State of the art. *Microbiol. Res.* **2018**, *212–213*, 38–58. [CrossRef] [PubMed]
155. Lin, D.M.; Koskella, B.; Lin, H.C. Phage therapy: An alternative to antibiotics in the age of multi-drug resistance. *World J. Gastrointest. Pharmacol. Ther.* **2017**, *8*, 162–173. [CrossRef]
156. Sulakvelidze, A.; Alavidze, Z.; Morris, J.G. Bacteriophage therapy. *Antimicrob. Agents Chemother.* **2001**, *45*, 649–659. [CrossRef]
157. Summers, W.C. The strange history of phage therapy. *Bacteriophage* **2012**, *2*, 130–133. [CrossRef]
158. Breitbart, M.; Bonnain, C.; Malki, K.; Sawaya, N.A. Phage puppet masters of the marine microbial realm. *Nat. Microbiol.* **2018**, *3*, 754–766. [CrossRef]
159. Bernstein, C.; Bernstein, H. DNA repair in bacteriophage. In *DNA Damage and Repair. Contemporary Cancer Research*; Nickoloff, J., Hoekstra, M., Eds.; Humana Press: Totowa, NJ, USA, 2001.
160. Kawacka, I.; Olejnik-schmidt, A.; Schmidt, M. Effectiveness of phage-based inhibition of *Listeria monocytogenes* in food products and food processing environments. *Microorganisms* **2020**, *8*, 1764. [CrossRef]
161. El-Shibiny, A.; El-Sahhar, S. Bacteriophages: The possible solution to treat infections caused by pathogenic bacteria. *Can. J. Microbiol.* **2017**, *63*, 865–879. [CrossRef]
162. Rios, A.; Moutinho, C.; Pinto, F.; Del Fiol, F.; Jozala, A.; Chaud, M.; Vila, M.; Teixeira, J.; Balcão, V. Alternatives to overcoming bacterial resistances: State-of-the-art. *Microbiol. Res.* **2016**, *191*, 51–80. [CrossRef]
163. Pereira, C.; Moreirinha, C.; Rocha, R.J.M.; Calado, R.; Romalde, J.L.; Nunes, M.L.; Almeida, A. Application of bacteriophages during depuration reduces the load of *Salmonella* Typhimurium in cockles. *Food Res. Int.* **2016**, *90*, 73–84. [CrossRef] [PubMed]
164. Pereira, C.; Moreirinha, C.; Teles, L.; Rocha, R.J.M.; Calado, R.; Romalde, J.L.; Nunes, M.L.; Almeida, A. Application of phage therapy during bivalve depuration improves *Escherichia coli* decontamination. *Food Microbiol.* **2017**, *61*, 102–112. [CrossRef] [PubMed]
165. Rong, R.; Lin, H.; Wang, J.; Khan, M.N.; Li, M.; Naseem, M.; Li, M.; Khan, M.N.; Li, M. Reductions of *Vibrio parahaemolyticus* in oysters after bacteriophage application during depuration. *Aquaculture* **2014**, *418–419*, 171–176. [CrossRef]
166. Duarte, J.; Pereira, C.; Costa, P.; Almeida, A. Bacteriophages with potential to inactivate *Aeromonas hydrophila* in cockles: In vitro and in vivo preliminary studies. *Antibiotics* **2021**, *10*, 710. [CrossRef]
167. Kalpage, M.; De Costa, D. Isolation of bacteriophages and determination of their efficiency in controlling *Ralstonia solanacearum* causing bacterial wilt of tomato. *Trop. Agric. Res.* **2014**, *26*, 140–151. [CrossRef]
168. Pinheiro, L.A.M.; Pereira, C.; Barreal, M.E.; Gallego, P.P.; Balcão, V.M.; Almeida, A. Use of phage ϕ6 to inactivate *Pseudomonas syringae* pv. *actinidiae* in kiwifruit plants: In vitro and ex vivo experiments. *Appl. Microbiol. Biotechnol.* **2020**, *104*, 1319–1330.
169. Rombouts, S.; Volckaert, A.; Venneman, S.; Declercq, B.; Vandenheuvel, D.; Allonsius, C.N.; Van Malderghem, C.; Jang, H.B.; Briers, Y.; Noben, J.P.; et al. Characterization of novel bacteriophages for biocontrol of bacterial blight in leek caused by *Pseudomonas syringae* pv. *porri*. *Front. Microbiol.* **2016**, *7*, 279. [CrossRef]
170. Pereira, C.; Costa, P.; Pinheiro, L.; Balcão, V.M.; Almeida, A. Kiwifruit bacterial canker: An integrative view focused on biocontrol strategies. *Planta* **2021**, *253*, 49. [CrossRef]
171. Beheshti Maal, K.; Delfan, A.S.; Salmanizadeh, S. Isolation and identification of two novel *Escherichia coli* bacteriophages and their application in wastewater treatment and coliform's phage therapy. *Jundishapur J. Microbiol.* **2015**, *8*, e14945. [CrossRef]
172. Withey, S.; Cartmell, E.; Avery, L.M.; Stephenson, T. Bacteriophages-Potential for application in wastewater treatment processes. *Sci. Total Environ.* **2005**, *339*, 1–18. [CrossRef]
173. Chanishvili, N. Phage therapy-history from Twort and d'Herelle through Soviet experience to current approaches. *Adv. Virus Res.* **2012**, *83*, 3–40. [PubMed]
174. Wu, J.-L.; Lin, H.-M.; Jan, L.; Hsu, Y.-L.; Chang, L.-H. Biological control of fish bacterial pathogen, *Aeromonas hydrophila*, by bacteriophage AH-1. *Fish. Pathol.* **1981**, *15*, 271–276. [CrossRef]
175. Kalatzis, P.G.; Bastías, R.; Kokkari, C.; Katharios, P. Isolation and characterization of two lytic bacteriophages, φst2 and φgrn1; Phage therapy application for biological control of *Vibrio alginolyticus* in aquaculture live feeds. *PLoS ONE* **2016**, *11*, e0151101. [CrossRef]
176. Yu, Y.P.; Gong, T.; Jost, G.; Liu, W.H.; Ye, D.Z.; Luo, Z.H. Isolation and characterization of five lytic bacteriophages infecting a *Vibrio* strain closely related to *Vibrio owensii*. *FEMS Microbiol. Lett.* **2013**, *348*, 112–119. [CrossRef] [PubMed]

177. Surekhamol, I.S.; Deepa, G.D.; Somnath Pai, S.; Sreelakshmi, B.; Varghese, S.; Bright Singh, I.S. Isolation and characterization of broad spectrum bacteriophages lytic to *Vibrio harveyi* from shrimp farms of Kerala, India. *Lett. Appl. Microbiol.* **2014**, *58*, 197–204. [CrossRef] [PubMed]
178. Lal, T.M.; Sano, M.; Ransangan, J. Isolation and characterization of large marine bacteriophage (*Myoviridae*), VhKM4 infecting *Vibrio harveyi*. *J. Aquat. Anim. Health* **2017**, *29*, 26–30. [CrossRef] [PubMed]
179. Kokkari, C.; Sarropoulou, E.; Bastias, R.; Mandalakis, M.; Katharios, P. Isolation and characterization of a novel bacteriophage infecting *Vibrio alginolyticus*. *Arch. Microbiol.* **2018**, *200*, 707–718. [CrossRef]
180. Nikapitiya, C.; Dananjaya, S.H.S.; Chandrarathna, H.P.S.U.; Senevirathne, A.; De Zoysa, M.; Lee, J. Isolation and characterization of multidrug resistance *Aeromonas salmonicida* subsp. *salmonicida* and its infecting novel phage ASP-1 from goldfish (Carassius auratus). *Indian J. Microbiol.* **2019**, *59*, 161–170.
181. Chandrarathna, H.P.S.U.; Nikapitiya, C.; Dananjaya, S.H.S.; De Silva, B.C.J.; Heo, G.J.; De Zoysa, M.; Lee, J. Isolation and characterization of phage AHP-1 and its combined effect with chloramphenicol to control *Aeromonas hydrophila*. *Braz. J. Microbiol.* **2020**, *51*, 409–416. [CrossRef]
182. Kazimierczak, J.; Wójcik, E.A.; Witaszewska, J.; Guziński, A.; Górecka, E.; Stańczyk, M.; Kaczorek, E.; Siwicki, A.K.; Dastych, J. Complete genome sequences of *Aeromonas* and *Pseudomonas* phages as a supportive tool for development of antibacterial treatment in aquaculture. *Virol. J.* **2019**, *16*, 4. [CrossRef]
183. Chen, F.; Sun, J.; Han, Z.; Yang, X.; Xian, J.A.A.; Lv, A.; Hu, X.; Shi, H. Isolation, identification and characteristics of *Aeromonas veronii* from diseased crucian carp (*Carassius auratus gibelio*). *Front. Microbiol.* **2019**, *10*, 2742. [CrossRef] [PubMed]
184. Stenholm, A.R.; Dalsgaard, I.; Middelboe, M. Isolation and characterization of bacteriophages infecting the fish pathogen *Flavobacterium psychrophilum*. *Appl. Environ. Microbiol.* **2008**, *74*, 4070–4078. [CrossRef] [PubMed]
185. Prasad, Y.; Kumar, D.; Sharma, A.K.; Nisha, D.; Ninawe, A.S. Isolation and efficacy characterizations of lytic bacteriophages against antibiotic resistant *Pseudomonas fluorescens* from sub-Himalayan region. *Biochem. Cell. Arch.* **2010**, *10*, 21–29.
186. Kim, J.H.; Gomez, D.K.; Nakai, T.; Park, S.C. Isolation and identification of bacteriophages infecting ayu *Plecoglossus altivelis* altivelis specific *Flavobacterium psychrophilum*. *Vet. Microbiol.* **2010**, *140*, 109–115. [CrossRef]
187. Crothers-Stomps, C.; Høj, L.; Bourne, D.G.; Hall, M.R.; Owens, L. Isolation of lytic bacteriophage against *Vibrio harveyi*. *J. Appl. Microbiol.* **2010**, *108*, 1744–1750. [CrossRef] [PubMed]
188. Phumkhachorn, P.; Rattanachaikunsopon, P. Isolation and partial characterization of a bacteriophage infecting the shrimp pathogen *Vibrio harveyi*. *Afr. J. Microbiol. Res.* **2010**, *4*, 1794–1800.
189. Yong, P.; Ding, Y.; Lin, H.; Wang, J. Isolation, identification and lysis properties analysis of a *Vibrio parahaemolyticus* phage VPp1. *Mar. Sci.* **2013**, *37*, 96–101.
190. Mateus, L.; Costa, L.; Silva, Y.J.; Pereira, C.; Cunha, A.; Almeida, A. Efficiency of phage cocktails in the inactivation of *Vibrio* in aquaculture. *Aquaculture* **2014**, *424–425*, 167–173. [CrossRef]
191. Prasad, Y.; Kumar, A.D. Isolation and efficacy evaluation of virulent bacteriophages specific to fish pathogenic bacterium, *Flavobacterium columnare*. *J. Appl. Anim. Res.* **2010**, *38*, 169–174. [CrossRef]
192. Li, Z.; Li, X.; Zhang, J.; Wang, X.; Wang, L.; Cao, Z.; Xu, Y. Use of phages to control *Vibrio splendidus* infection in the juvenile sea cucumber *Apostichopus japonicus*. *Fish. Shellfish Immunol.* **2016**, *54*, 302–311. [CrossRef]
193. Wang, S.T.; Meng, X.Z.; Li, L.S.; Dang, Y.F.; Fang, Y.; Shen, Y.; Xu, X.Y.; Wang, R.Q.; Li, J.-L. Biological parameters, immune enzymes, and histological alterations in the livers of grass carp infected with *Aeromonas hydrophila*. *Fish. Shellfish Immunol.* **2017**, *70*, 121–128. [CrossRef] [PubMed]
194. Laanto, E.; Bamford, J.K.H.; Ravantti, J.J.; Sundberg, L.R. The use of phage FCL-2 as an alternative to chemotherapy against columnaris disease in aquaculture. *Front. Microbiol.* **2015**, *6*, 829. [CrossRef] [PubMed]
195. Wu, J.-L.; Chao, W.-J. Isolation and application of a new bacteriophages, ϕET-1, which infects *Edwardsiella tarda*, the pathogen of edwardsiellosis. *Fish. Dis. Res.* **1982**, *4*, 8–17.
196. Nakai, T.; Sugimoto, R.; Park, K.H.; Matsuoka, S.; Mori, K.; Nishioka, T.; Maruyama, K. Protective effects of bacteriophage on experimental *Lactococcus garvieae* infection in yellowtail. *Dis. Aquat. Organ.* **1999**, *37*, 33–41. [CrossRef]
197. Park, S.E.C.; Shimamura, I.; Fukunaga, M.; Mori, K.; Nakai, T. Isolation of bacteriophages specific to a fish pathogen, *Pseudomonas plecoglossicida*, as a candidate for disease control. *Appl. Environ. Microbiol.* **2000**, *66*, 1416–1422. [CrossRef]
198. Park, S.C.; Nakai, T. Bacteriophage control of *Pseudomonas plecoglossicida* infection in ayu *Plecoglossus altivelis*. *Dis. Aquat. Organ.* **2003**, *53*, 33–39. [CrossRef]
199. Madsen, L.; Bertelsen, S.K.; Dalsgaard, I.; Middelboe, M. Dispersal and survival of *Flavobacterium psychrophilum* phages in vivo in rainbow trout and in vitro under laboratory conditions: Implications for their use in phage therapy. *Appl. Environ. Microbiol.* **2013**, *79*, 4853–4861. [CrossRef]
200. Christiansen, R.H.; Madsen, L.; Dalsgaard, I.; Middelboe, M. Effect of bacteriophages on the growth of *Flavobacterium psychrophilum* and development of phage-resistant strains. *Microb. Ecol.* **2008**, *71*, 845–859. [CrossRef]
201. Ren, H.; Li, Z.; Xu, Y.; Wang, L.; Li, X. Protective effectiveness of feeding phage cocktails in controlling *Vibrio parahaemolyticus* infection of sea cucumber *Apostichopus japonicus*. *Aquaculture* **2019**, *503*, 322–329. [CrossRef]
202. Richards, G.P. Bacteriophage remediation of bacterial pathogens in aquaculture: A review of the technology. *Bacteriophage* **2014**, *4*, e975540. [CrossRef]

203. Intralytix Inc. Bacteriophages Products. Available online: http://www.intralytix.com/index.php?page=prod (accessed on 3 November 2020).
204. Mattey, M. Treatment of Bacterial Infections in Aquaculture. 2018. Available online: https://patents.google.com/patent/WO2016170013A1/en (accessed on 3 November 2021).
205. ACD Pharma. CUSTUS®YRS: Bacteriophages against Yersiniosis. Available online: https://acdpharma.com/custusyrs-eng/ (accessed on 3 November 2021).
206. Mangalore Biotech Laboratory. Mangalore Biotech Lab: Products. Available online: http://mangalorebiotech.com (accessed on 3 November 2021).
207. Letchumanan, V.; Chan, K.G.; Pusparajah, P.; Saokaew, S.; Duangjai, A.; Goh, B.H.; Ab Mutalib, N.S.; Lee, L.H. Insights into bacteriophage application in controlling *Vibrio* species. *Front. Microbiol.* **2016**, *7*, 1114. [CrossRef] [PubMed]
208. Aquatic Biologicals. Eco-Friendly Innovative Solutions for Aquaculture Health. Available online: https://www.aquatic-biologicals.com/ (accessed on 3 November 2021).
209. Jun, J.W.; Kim, H.J.; Shin, S.P.; Han, J.E.; Chai, J.Y.; Park, S.C. Protective effects of the *Aeromonas* phages pAh1-C and pAh6-C against mass mortality of the cyprinid loach (*Misgurnus anguillicaudatus*) caused by *Aeromonas hydrophila*. *Aquaculture* **2013**, *416–417*, 289–295. [CrossRef]
210. Wang, J.B.; Lin, N.T.; Tseng, Y.H.; Weng, S.F. Genomic characterization of the novel *Aeromonas hydrophila* phage ahp1 suggests the derivation of a new subgroup from phiKMV-Like family. *PLoS ONE* **2016**, *11*, e0162060. [CrossRef] [PubMed]
211. Easwaran, M.; Dananjaya, S.H.S.; Park, S.C.; Lee, J.; Shin, H.J.; De Zoysa, M. Characterization of bacteriophage pAh-1 and its protective effects on experimental infection of *Aeromonas hydrophila* in zebrafish (*Danio rerio*). *J. Fish. Dis.* **2017**, *40*, 841–846. [CrossRef] [PubMed]
212. Hoang, H.A.; Xuan, T.T.T.; Nga, L.P.; Oanh, D.T.H. Selection of phages to control *Aeromonas hydrophila*—An infectious agent in striped catfish. *Biocontrol Sci.* **2019**, *24*, 23–28. [CrossRef]
213. Tu, V.Q.; Nguyen, T.T.; Tran, X.T.T.; Millard, A.D.; Phan, H.T.; Le, N.P.; Dang, O.T.H.; Hoang, H.A. Complete genome sequence of a novel lytic phage infecting *Aeromonas hydrophila*, an infectious agent in striped catfish (*Pangasianodon hypophthalmus*). *Arch. Virol.* **2020**, *165*, 2973–2977. [CrossRef]
214. Cheng, Y.; Gao, D.; Xia, Y.; Wang, Z.; Bai, M.; Luo, K.; Cui, X.; Wang, Y.; Zhang, S.; Xiao, W. Characterization of novel bacteriophage AhyVDH1 and its lytic activity against *Aeromonas hydrophila*. *Curr. Microbiol.* **2021**, *78*, 329–337. [CrossRef]
215. Kim, J.H.; Son, J.S.; Choi, Y.J.; Choresca, C.H.; Shin, S.P.; Han, J.E.; Jun, J.W.; Kang, D.H.; Oh, C.; Heo, S.J.; et al. Isolation and characterization of a lytic *Myoviridae* bacteriophage PAS-1 with broad infectivity in *Aeromonas salmonicida*. *Curr. Microbiol.* **2012**, *64*, 418–426. [CrossRef]
216. Rodgers, C.; Pringle, J.; Mccarthyi, D.; Austin, B. Quantitative and qualitative studies of *Aeromonas salmonicida* bacteriophage. *J. Gen. Microbiol.* **1981**, *125*, 335–345. [CrossRef]
217. Chen, L.; Yuan, S.; Liu, Q.; Mai, G.; Yang, J.; Deng, D.; Zhang, B.; Liu, C.; Ma, Y. In vitro design and evaluation of phage cocktails against *Aeromonas salmonicida*. *Front. Microbiol.* **2018**, *9*, 1476. [CrossRef]
218. Imbeault, S.; Parent, S.; Lagacé, M.; Uhland, C.F.; Blais, J. Using bacteriophages to prevent furunculosis caused by *Aeromonas salmonicida* in farmed brook trout. *J. Aquat. Anim. Health* **2006**, *18*, 203–214. [CrossRef]
219. Verner–Jeffreys, D.W.; Algoet, M.; Pond, M.J.; Virdee, H.K.; Bagwell, N.J.; Roberts, E.G. Furunculosis in Atlantic salmon (*Salmo salar* L.) is not readily controllable by bacteriophage therapy. *Aquaculture* **2007**, *270*, 475–484. [CrossRef]
220. Kim, J.H.; Choresca, C.H.; Shin, S.P.; Han, J.E.; Jun, J.W.; Park, S.C. Biological control of *Aeromonas salmonicida* subsp. salmonicida infection in rainbow trout (*Oncorhynchus mykiss*) using *Aeromonas* phage PAS-1. *Transbound. Emerg. Dis.* **2015**, *62*, 81–86. [CrossRef] [PubMed]
221. Madhusudana Rao, B.; Lalitha, K.V. Bacteriophages for aquaculture: Are they beneficial or inimical. *Aquaculture* **2015**, *437*, 146–154. [CrossRef]
222. Paquet, V.E.; Vincent, A.T.; Moineau, S.; Charette, S.J. Beyond the A-layer: Adsorption of lipopolysaccharides and characterization of bacteriophage-insensitive mutants of *Aeromonas salmonicida* subsp. *salmonicida*. *Mol. Microbiol.* **2019**, *112*, 667–677. [CrossRef]
223. Nakai, T. Application of bacteriophages for control of infectious diseases in aquaculture. In *Bacteriophages in the Control of Food and Waterborne Pathogens*; Sabour, P., Griffiths, M., Eds.; ASM Press: Washington, DC, USA, 2010; pp. 257–272.
224. Kowalska, J.D.; Kazimierczak, J.; Sowińska, P.M.; Wójcik, E.A.; Siwicki, A.K.; Dastych, J. Growing trend of fighting infections in aquaculture environment—Opportunities and challenges of phage therapy. *Antibiotics* **2020**, *9*, 301. [CrossRef]
225. Altamirano, F.; Barr, J. Phage therapy in the postantibiotic era. *Clin. Microbiol. Rev.* **2019**, *32*, e00066-18.
226. Alavidze, Z.; Aminov, R.; Betts, A.; Bardiau, M.; Bretaudeau, L.; Caplin, J.; Chanishvili, N.; Coffey, A.; Cooper, I.; De Vos, D.; et al. Silk route to the acceptance and re-implementation of bacteriophage therapy. *Biotechnol. J.* **2016**, *11*, 595–600.
227. Emerson, J.B.; Thomas, B.C.; Andrade, K.; Allen, E.E.; Heidelberg, K.B.; Banfielda, J.F. Dynamic viral populations in hypersaline systems as revealed by metagenomic assembly. *Appl. Environ. Microbiol.* **2012**, *78*, 6309–6320. [CrossRef]
228. Ross, A.; Ward, S.; Hyman, P. More is better: Selecting for broad host range bacteriophages. *Front. Microbiol.* **2016**, *7*, 1352. [CrossRef]
229. Pérez-Sánchez, T.; Mora-Sánchez, B.; Balcázar, J.L. Biological approaches for disease control in aquaculture: Advantages, limitations and challenges. *Trends Microbiol.* **2018**, *26*, 896–903. [CrossRef] [PubMed]

230. Wang, J.-B.; Yu, M.-S.; Tseng, T.-T.; Lin, L.-C. Molecular characterization of Ahp2, a lytic bacteriophage of *Aeromonas hydrophila*. *Viruses* **2021**, *13*, 477. [CrossRef] [PubMed]
231. Nithin, M.; Girisha, S.; Kushala, K.; Chandan, D.; Puneeth, T.; Kumar, N.; Vinay, T.; Suresh, T.; Lopamudra, S.; Ramesh, K. Novel lytic bacteriophages (AhFM4 & AhFM5) as bio-control measures against multidrug resistant biofilm producing *Aeromonas hydrophila* (AhZ1K). *Aquaculture* **2021**, *544*, 737106.
232. Børsheim, K. Native marine bacteriophages. *FEMS Microbiol. Ecol.* **1993**, *102*, 141–159. [CrossRef]
233. Kellogg, C.A.; Rose, J.B.; Jiang, S.C.; Thurmond, J.M.; Paul, J.H. Genetic diversity of related vibriophages isolated from marine environments around Florida and Hawaii, USA. *Mar. Ecol. Prog. Ser.* **1995**, *120*, 89–98. [CrossRef]
234. Wichels, A.; Biel, S.S.; Gelderblom, H.R.; Brinkhoff, T.; Muyzer, G.; Schütt, C. Bacteriophage diversity in the North Sea. *Appl. Environ. Microbiol.* **1998**, *64*, 4128–4133. [CrossRef]
235. Pallavi, B.; Puneeth, T.G.; Shekar, M.; Girisha, S.K. Isolation, characterization and genomic analysis of vB-AhyM-AP1, a lytic bacteriophage infecting *Aeromonas hydrophila*. *J. Appl. Microbiol.* **2021**, *131*, 695–705. [CrossRef]
236. Liu, J.; Gao, S.; Dong, Y.; Lu, C.; Liu, Y. Isolation and characterization of bacteriophages against virulent *Aeromonas hydrophila*. *BMC Microbiol.* **2020**, *20*, 141. [CrossRef]
237. Pereira, C.; Silva, Y.J.; Santos, A.L.; Cunha, Â.; Gomes, N.C.M.; Almeida, A. Bacteriophages with potential for inactivation of fish pathogenic bacteria: Survival, host specificity and effect on bacterial community structure. *Mar. Drugs* **2011**, *9*, 2236–2255. [CrossRef]
238. Golais, F.; Hollý, J.; Vítkovská, J. Coevolution of bacteria and their viruses. *Folia Microbiol.* **2013**, *58*, 177–186. [CrossRef]
239. Koskella, B.; Meaden, S. Understanding bacteriophage specificity in natural microbial communities. *Viruses* **2013**, *5*, 806–823. [CrossRef] [PubMed]
240. Mirzaei, K.M.; Nilsson, A.S. Isolation of phages for phage therapy: A comparison of spot tests and efficiency of plating analyses for determination of host range and efficacy. *PLoS ONE* **2015**, *10*, e0118557. [CrossRef] [PubMed]
241. Shao, Y.; Wang, I.-N. Bacteriophage adsorption rate and optimal lysis time. *Genetics* **2008**, *180*, 471–482. [CrossRef] [PubMed]
242. Wang, I.N. Lysis timing and bacteriophage fitness. *Genetics* **2006**, *172*, 17–26. [CrossRef]
243. Storms, Z.; Arsenault, E.; Sauvageau, D.; Cooper, D. Bacteriophage adsorption efficiency and its effect on amplification. *Bioprocess. Biosyst. Eng.* **2010**, *33*, 823–831. [CrossRef]
244. Weinbauer, M.G. Ecology of prokaryotic viruses. *FEMS Microbiol. Rev.* **2004**, *28*, 127–181. [CrossRef]
245. Dalmasso, M.; Strain, R.; Neve, H.; Franz, C.M.A.P.; Cousin, F.J.; Ross, R.P.; Hill, C. Three new *Escherichia coli* phages from the human gut show promising potential for phage therapy. *PLoS ONE* **2016**, *11*, e0156773. [CrossRef]
246. Abedon, S.T.; Thomas-Abedon, C. Phage therapy pharmacology. *Curr. Pharm. Biotechnol.* **2010**, *11*, 28–47. [CrossRef]
247. Abedon, S.T. Lysis from without. *Bacteriophage* **2011**, *1*, 46–49. [CrossRef]
248. Abedon, S.T.; Culler, R.R. Bacteriophage evolution given spatial constraint. *J. Theor. Biol.* **2007**, *248*, 111–119. [CrossRef]
249. Ly-Chatain, M.H. The factors affecting effectiveness of treatment in phages therapy. *Front. Microbiol.* **2014**, *5*, 51. [CrossRef] [PubMed]
250. Jończyk, E.; Kłak, M.; Międzybrodzki, R.; Górski, A. The influence of external factors on bacteriophages—Review. *Folia Microbiol.* **2011**, *56*, 191–200. [CrossRef] [PubMed]
251. Maura, D.; Debarbieux, L. Bacteriophages as twenty-first century antibacterial tools for food and medicine. *Appl. Microbiol. Biotechnol.* **2011**, *90*, 851–859. [CrossRef] [PubMed]
252. Silva, Y.; Costa, L.; Pereira, C.; Cunha, A.; Calado, R.; Gomes, N.; Almeida, A. Influence of environmental variables in the efficiency of phage therapy in aquaculture. *Microb. Biotechnol.* **2014**, *7*, 401–413. [CrossRef]
253. Ackermann, H.-W.; Tremblay, D.; Moineau, S. Long-term bacteriophage preservation. *WFCC Newsl.* **2004**, *38*, 35–40.
254. Obradovic, A.; Jones, J.B.; Momol, M.T.; Balogh, B.; Olson, S.M. Management of tomato bacterial spot in the field by foliar applications of bacteriophages and SAR inducers. *Plant. Dis.* **2004**, *88*, 736–740. [CrossRef]
255. Pinheiro, L.; Pereira, C.; Frazão, C.; Balcão, V.; Almeida, A. Efficiency of phage φ6 for biocontrol of *Pseudomonas syringae* pv. *syringae*: An in vitro preliminary study. *Microorganisms* **2019**, *7*, 1319–1330.
256. Mojica, K.D.A.; Brussaard, C.P.D. Factors affecting virus dynamics and microbial host-virus interactions in marine environments. *FEMS Microbiol. Ecol.* **2014**, *89*, 495–515. [CrossRef]
257. Tey, B.T.; Ooi, S.T.; Yong, K.C.; Yeen, M.; Ng, T.; Ling, T.C.; Siang Tan, W. Production of fusion m13 phage bearing the di-sulphide constrained peptide sequence (C-WSFFSNI-C) that interacts with hepatitis B core antigen. *Afr. J. Biotechnol.* **2009**, *8*, 268–273.
258. Leverentz, B.; Conway, W.S.; Janisiewicz, W.; Camp, M.J. Optimizing concentration and timing of a phage spray application to reduce *Listeria monocytogenes* on honeydew melon tissue. *J. Food Prot.* **2004**, *67*, 1682–1686. [CrossRef]
259. Leverentz, B.; Conway, W.S.; Alavidze, Z.; Janisiewicz, W.J.; Fuchs, Y.; Camp, M.J.; Chighladze, E.; Sulakvelidze, A. Examination of bacteriophage as a biocontrol method for *Salmonella* on fresh-cut fruit: A model study. *J. Food Prot.* **2001**, *64*, 1116–1121. [CrossRef] [PubMed]
260. Pirisi, A. Phage therapy—Advantages over antibiotics? *Lancet* **2000**, *356*, 1418. [CrossRef]
261. Xuan, T.; Hoang, H.A.; Tam, L. Stability and activity of TG25P phage in control of *Aeromonas hydrophila* in striped catfish pond water. *Sci. Technol. Dev. J.* **2018**, *21*, 64–70. [CrossRef]
262. Baross, J.A.; Liston, J.; Morita, R.Y. Incidence of *Vibrio parahaemolyticus* bacteriophages and other *Vibrio* bacteriophages in marine samples. *Appl. Environ. Microbiol.* **1978**, *36*, 492–499. [CrossRef]

263. Fennema, O. *Food Chemistry*, 3rd ed.; Marcel Dekker, Inc.: New York, NY, USA, 1996.
264. Buerger, P.; Weynberg, K.D.; Wood-Charlson, E.M.; Sato, Y.; Willis, B.L.; Van Oppen, M.J.H. Novel T4 bacteriophages associated with black band disease in corals. *Environ. Microbiol.* **2019**, *21*, 1969–1979. [CrossRef]
265. Hudson, J.A.; Billington, C.; Carey-Smith, G.; Greening, G. Bacteriophages as biocontrol agents in food. *J. Food Prot.* **2005**, *68*, 426–437. [CrossRef]
266. Jacquemot, L.; Bettarel, Y.; Monjol, J.; Corre, E.; Halary, S.; Desnues, C.; Bouvier, T.; Ferrier-Pagès, C.; Baudoux, A.-C. Therapeutic potential of a new jumbo phage that infects *Vibrio coralliilyticus*, a widespread coral pathogen. *Front. Microbiol.* **2018**, *9*, 2501. [CrossRef]
267. Kowalski, W.J.; Bahnfleth, W.P.; Hernandez, M.T. A genomic model for predicting the ultraviolet susceptibility of viruses and bacteria. In Proceedings of the 21st International Conference, Caise 2009, Amsterdam, The Netherlands, 8–12 June 2009; Volume 11, pp. 15–28.
268. Hotze, E.M.; Badireddy, A.R.; Chellam, S.; Wiesner, M.R. Mechanisms of bacteriophage inactivation via singlet oxygen generation in UV illuminated fullerol suspensions. *Environ. Sci. Technol.* **2009**, *43*, 6639–6645. [CrossRef]
269. Wigginton, K.R.; Menin, L.; Montoya, J.P.; Kohn, T. Oxidation of virus proteins during UV254 and singlet oxygen mediated inactivation. *Environ. Sci. Technol.* **2010**, *44*, 5437–5443. [CrossRef]
270. Lytle, C.D.; Sagripanti, J.-L. Predicted inactivation of viruses of relevance to biodefense by solar radiation. *J. Virol.* **2005**, *79*, 14244–14252. [CrossRef]
271. Tseng, C.C.; Li, C.S. Inactivation of virus-containing aerosols by ultraviolet germicidal irradiation. *Aerosol Sci. Technol.* **2005**, *39*, 1136–1142. [CrossRef]
272. Turgeon, N.; Toulouse, M.-J.; Martel, B.; Moineau, S.; Duchaine, C. Comparison of five bacteriophages as models for viral aerosol studies. *Appl. Environ. Microbiol.* **2014**, *80*, 4242–4250. [CrossRef] [PubMed]
273. Vasickova, P.; Kovarcik, K. Natural persistence of food and waterborne viruses. In *Viruses in Food and Water-Risks, Surveillance and Control*; Cook, N., Ed.; Woodhead Publishing Limited: Philadelphia, PA, USA, 2013; pp. 179–204.
274. Verreault, D.; Marcoux-Voiselle, M.; Turgeon, N.; Moineau, S.; Duchaine, C. Resistance of aerosolized bacterial viruses to relative humidity and temperature. *Appl. Environ. Microbiol.* **2015**, *81*, 7305–7311. [CrossRef] [PubMed]
275. Żaczek, M.; Weber-Dabrowska, B.; Górski, A. Phages as a cohesive prophylactic and therapeutic approach in aquaculture systems. *Antibiotics* **2020**, *9*, 564. [CrossRef] [PubMed]
276. Phumkhachorn, P.; Rattanachaikunsopon, P. Use of bacteriophage to control experimental *Aeromonas hydrophila* infection in tilapia (*Oreochromis niloticus*). *Pak. J. Biol. Sci.* **2020**, *23*, 1659–1665. [CrossRef] [PubMed]
277. Dela Cruz-Papa, D.M.A.; Candare, C.M.G.; Cometa, G.L.S.; Gudez, D.E.G.; Guevara, A.M.I.T.; Relova, M.B.T.G.; Papa, R.D.S. *Aeromonas hydrophila* bacteriophage UP87: An alternative to antibiotic treatment for motile *Aeromonas* septicemia in Nile tilapia (*Oreochromis niloticus*). *Philipp. Agric. Sci.* **2014**, *97*, 96–101.
278. Huang, K.; Nitin, N. Edible bacteriophage based antimicrobial coating on fish feed for enhanced treatment of bacterial infections in aquaculture industry. *Aquaculture* **2019**, *502*, 18–25. [CrossRef]
279. Vonasek, E.; Le, P.; Nitin, N. Encapsulation of bacteriophages in whey protein films for extended storage and release. *Food Hydrocoll.* **2014**, *37*, 7–13. [CrossRef]
280. Labrie, S.J.; Samson, J.E.; Moineau, S. Bacteriophage resistance mechanisms. *Nat. Rev. Microbiol.* **2010**, *8*, 317–327. [CrossRef]
281. Heller, K.J. Molecular interaction between bacteriophage and the gram.negative cell envelope. *Arch. Microbiol.* **1992**, *158*, 235–248. [CrossRef]
282. O'Flynn, G.; Ross, R.P.; Fitzgerald, G.F.; Coffey, A. Evaluation of a cocktail of three bacteriophages for biocontrol of *Escherichia coli* O157:H7. *Appl. Environ. Microbiol.* **2004**, *70*, 3417–3424. [CrossRef] [PubMed]
283. Tanji, Y.; Shimada, T.; Yoichi, M.; Miyanaga, K.; Hori, K.; Unno, H. Toward rational control of *Escherichia coli* O157:H7 by a phage cocktail. *Appl. Microbiol. Biotechnol.* **2004**, *64*, 270–274. [CrossRef] [PubMed]
284. Bohannan, B.J.M.; Travisano, M.; Lenski, R.E. Epistatic interactions can lower the cost of resistance to multiple consumers. *Evolution* **1999**, *53*, 292–295. [CrossRef] [PubMed]
285. Brockhurst, M.A.; Buckling, A.; Rainey, P.B. The effect of a bacteriophage on diversification of the opportunistic bacterial pathogen, *Pseudomonas aeruginosa*. *Proc. Biol. Sci.* **2005**, *272*, 1385–1391. [CrossRef] [PubMed]
286. Lennon, J.T.; Khatana, S.A.M.; Marston, M.F.; Martiny, J.B.H. Is there a cost of virus resistance in marine cyanobacteria? *ISME J.* **2007**, *1*, 300–312. [CrossRef]
287. Quance, M.A.; Travisano, M. Effects of temperature on the fitness cost of resistance to bacteriophage T4 in *Escherichia coli*. *Evolution* **2009**, *63*, 1406–1416. [CrossRef] [PubMed]
288. Koskella, B.; Brockhurst, M.A. Bacteria-phage coevolution as a driver of ecological and evolutionary processes in microbial communities. *FEMS Microbiol. Rev.* **2014**, *38*, 916–931. [CrossRef]
289. Scanlan, P.D.; Buckling, A.; Hall, A.R. Experimental evolution and bacterial resistance: (Co)evolutionary costs and trade-offs as opportunities in phage therapy research. *Bacteriophage* **2015**, *5*, e1050153. [CrossRef]
290. Moreirinha, C.; Osório, N.; Pereira, C.; Simões, S.; Delgadillo, I.; Almeida, A. Protein expression modifications in phage-resistant mutants of *Aeromonas salmonicida* after AS-A phage treatment. *Antibiotics* **2018**, *7*, 21. [CrossRef]

291. Górski, A.; Międzybrodzki, R.; Łobocka, M.; Głowacka-Rutkowska, A.; Bednarek, A.; Borysowski, J.; Jończyk-Matysiak, E.; Łusiak-Szelachowska, M.; Weber-Dabrowska, B.; Bagińska, N.; et al. Phage therapy: What have we learned? *Viruses* **2018**, *10*, 288. [CrossRef]
292. Archana, A.; Patel, P.S.; Kumar, R.; Nath, G. Neutralizing antibody response against subcutaneously injected bacteriophages in rabbit model. *Virus Dis.* **2021**, *32*, 38–45. [CrossRef] [PubMed]
293. Ramos-Vivas, J.; Superio, J.; Galindo-Villegas, J.; Acosta, F. Phage therapy as a focused management strategy in aquaculture. *Int. J. Mol. Sci.* **2021**, *22*, 10436. [CrossRef] [PubMed]
294. Yun, S.; Jun, J.W.; Giri, S.S.; Kim, H.J.; Chi, C.; Kim, S.G.; Kim, S.W.; Kang, J.W.; Han, S.J.; Kwon, J.; et al. Immunostimulation of *Cyprinus carpio* using phage lysate of *Aeromonas hydrophila*. *Fish. Shellfish Immunol.* **2019**, *86*, 680–687. [CrossRef] [PubMed]
295. Krut, O.; Bekeredjian-Ding, I. Contribution of the immune response to phage therapy. *J. Immunol.* **2018**, *200*, 3037–3044. [CrossRef] [PubMed]
296. Weber-Dabrowska, B.; Zimecki, M.; Mulczyk, M. Effective phage therapy is associated with normalization of cytokine production by blood cell cultures. *Arch. Immunol. Ther. Exp.* **2000**, *48*, 31–37.
297. Henein, A. What are the limitations on the wider therapeutic use of phage? *Bacteriophage* **2013**, *3*, e24872. [CrossRef] [PubMed]
298. Colavecchio, A.; Goodridge, L.D. Phage therapy approaches to reducing pathogen persistence and transmission in animal production environments: Opportunities and challenges. *Preharvest Food Saf.* **2018**, 291–308.
299. Kalatzis, P.G.; Castillo, D.; Katharios, P.; Middelboe, M. Bacteriophage interactions with marine pathogenic vibrios: Implications for phage therapy. *Antibiotics* **2018**, *7*, 15. [CrossRef]
300. Criscuolo, E.; Spadini, S.; Lamanna, J.; Ferro, M.; Burioni, R. Bacteriophages and their immunological applications against infectious threats. *J. Immunol. Res.* **2017**, *2017*, 3780697. [CrossRef]
301. Merril, C.R.; Biswas, B.; Carlton, R.; Jensen, N.C.; Creed, G.J.; Zullo, S.; Adhya, S. Long-circulating bacteriophage as antibacterial agents. *Proc. Natl. Acad. Sci. USA* **1996**, *93*, 3188–3192. [CrossRef]
302. Górski, A.; Jończyk-Matysiak, E.; Łusiak-Szelachowska, M.; Międzybrodzki, R.; Weber-Dąbrowska, B.; Borysowski, J. The potential of phage therapy in sepsis. *Front. Immunol.* **2017**, *8*, 1783. [CrossRef] [PubMed]
303. Schulz, P.; Pajdak-Czaus, J.; Robak, S.; Dastych, J.; Siwicki, A.K. Bacteriophage-based cocktail modulates selected immunological parameters and post-challenge survival of rainbow trout (*Oncorhynchus mykiss*). *J. Fish. Dis.* **2019**, *42*, 1151–1160. [CrossRef] [PubMed]
304. Schulz, P.; Robak, S.; Dastych, J.; Siwicki, A.K. Influence of bacteriophages cocktail on European eel (*Anguilla anguilla*) immunity and survival after experimental challenge. *Fish. Shellfish Immunol.* **2019**, *84*, 28–37. [CrossRef] [PubMed]
305. Kumar, R.; Clermont, G.; Vodovotz, Y.; Chow, C.C. The dynamics of acute inflammation. *J. Theor. Biol.* **2004**, *230*, 145–155. [CrossRef]
306. Muniesa, M.; Colomer-Lluch, M.; Jofre, J. Potential impact of environmental bacteriophages in spreading antibiotic resistance genes. *Future Microbiol.* **2013**, *8*, 739–751. [CrossRef] [PubMed]
307. Payne, R.; Jansen, V. Pharmacokinetic principles of bacteriophage therapy. *Clin. Pharmacokinet.* **2003**, *42*, 315–325. [CrossRef]
308. Koppang, E.O.; Fjølstad, M.; Melgård, B.; Vigerust, M.; Sørum, H. Non-pigment-producing isolates of *Aeromonas salmonicida* subspecies *salmonicida*: Isolation, identification, transmission and pathogenicity in Atlantic salmon, *Salmo salar* L. *J. Fish Dis.* **2000**, *23*, 39–48. [CrossRef]
309. Kim, D.H.; Choi, S.Y.; Kim, C.S.; Oh, M.J.; Jeong, H.D. Low-value fish used as feed in aquaculture were a source of furunculosis caused by atypical *Aeromonas salmonicida*. *Aquaculture* **2013**, *408–409*, 113–117. [CrossRef]
310. Coscelli, G.A.; Bermúdez, R.; Sancho Silva, A.R.; Ruíz de Ocenda, M.V.; Quiroga, M.I. Granulomatous dermatitis in turbot (*Scophthalmus maximus* L.) associated with natural *Aeromonas salmonicida* subsp. *salmonicida infection*. *Aquaculture* **2014**, *428–429*, 111–116. [CrossRef]
311. Li, T.; Long, M.; Ji, C.; Shen, Z.; Gatesoupe, F.J.; Zhang, X.; Zhang, Q.; Zhang, L.; Zhao, Y.; Liu, X.; et al. Alterations of the gut microbiome of largemouth bronze gudgeon (*Coreius guichenoti*) suffering from furunculosis. *Sci. Rep.* **2016**, *6*, 30606. [CrossRef]
312. Fernández-Álvarez, C.; Gijón, D.; Álvarez, M.; Santos, Y. First isolation of *Aeromonas salmonicida* subspecies *salmonicida* from diseased sea bass, *Dicentrarchus labrax* (L.), cultured in Spain. *Aquac. Rep.* **2016**, *4*, 36–41. [CrossRef]
313. Bartkova, S.; Kokotovic, B.; Skall, H.F.; Lorenzen, N.; Dalsgaard, I. Detection and quantification of *Aeromonas salmonicida* in fish tissue by real-time PCR. *J. Fish Dis.* **2017**, *40*, 231–242. [CrossRef] [PubMed]
314. Chenia, H.Y.; Duma, S. Characterization of virulence, cell surface characteristics and biofilm-forming ability of *Aeromonas* spp. isolates from fish and sea water. *J. Fish Dis.* **2017**, *40*, 339–350. [CrossRef] [PubMed]
315. Duman, M.; Saticioglu, I.B.; Janda, J.M.; Altun, S. The determination of the infectious status and prevalence of motile *Aeromonas* species isolated from disease cases in rainbow trout (*Oncorhynchus mykiss*) and aquarium fish. *J. Fish Dis.* **2018**, *41*, 1843–1857. [CrossRef] [PubMed]
316. Delalay, G.; Berezowski, J.; Diserens, N.; Schmidt-Posthaus, H. Characteristics of bacterial isolates in swiss farmed and ornamental fish from a retrospective study from 2000 to 2017. *Schweiz. Arch. Tierheilkd.* **2018**, *161*, 43–57. [CrossRef]
317. Du, X.; Bayliss, S.C.; Feil, E.J.; Liu, Y.; Wang, C.; Zhang, G.; Zhou, D.; Wei, D.; Tang, N.; Leclercq, S.O.; et al. Real time monitoring of *Aeromonas salmonicida* evolution in response to successive antibiotic therapies in a commercial fish farm. *Environ. Microbiol.* **2019**, *21*, 1113–1123. [CrossRef]

318. Fu, S.; Ni, P.; Wang, Y.; Jin, S.; Jiang, Z.; Ye, S.; Li, R. Delineating the origins of the multidrug-resistant pathogens in ornamental fish farms by multilocus sequence typing and identification of a novel multidrug-resistant plasmid. *Can. J. Microbiol.* **2019**, *65*, 551–562. [CrossRef]
319. Dalsgaard, I.; Madsen, L. Bacterial pathogens in rainbow trout, *Oncorhynchus mykiss* (Walbaum), reared at Danish freshwater farms. *J. Fish Dis.* **2000**, *23*, 199–209. [CrossRef]
320. Rupp, M.; Knüsel, R.; Sindilariu, P.D.; Schmidt-Posthaus, H. Identification of important pathogens in European perch (*Perca fluviatilis*) culture in recirculating aquaculture systems. *Aquac. Int.* **2019**, *27*, 1045–1053. [CrossRef]
321. Massicotte, M.A.; Vincent, A.T.; Schneider, A.; Paquet, V.E.; Frenette, M.; Charette, S.J. One *Aeromonas salmonicida* subsp. *salmonicida* isolate with a pAsa5 variant bearing antibiotic resistance and a pRAS3 variant making a link with a swine pathogen. *Sci. Total Environ.* **2019**, *690*, 313–320.
322. Sørum, H.; Holstad, G.; Lunder, T.; Håstein, T. Grouping by plasmid profiles of atypical *Aeromonas salmonicida* isolated from fish, with special reference to salmonid fish. *Dis. Aquat. Organ.* **2000**, *41*, 159–171. [CrossRef] [PubMed]
323. Lund, V.; Jenssen, L.M.; Wesmajervi, M.S. Assessment of genetic variability and relatedness among atypical *Aeromonas salmonicida* from marine fishes, using AFLP-fingerprinting. *Dis. Aquat. Organ.* **2002**, *50*, 119–126. [CrossRef] [PubMed]
324. Giraud, E. Mechanisms of quinolone resistance and clonal relationship among *Aeromonas salmonicida* strains isolated from reared fish with furunculosis. *J. Med. Microbiol.* **2004**, *53*, 895–901. [CrossRef] [PubMed]
325. Pylkkö, P.; Pohjanvirta, T.; Madetoja, J.; Pelkonen, S. Characterisation of atypical *Aeromonas salmonicida* infection in Arctic charr *Salvelinus alpinus* and European grayling *Thymallus thymallus*. *Dis. Aquat. Organ.* **2005**, *66*, 121–128. [CrossRef]
326. Nam, I.Y.; Joh, K. Rapid detection of virulence factors of *Aeromonas* isolated from a trout farm by hexaplex-PCR. *J. Microbiol.* **2007**, *45*, 297–304.
327. Pedersen, K.; Skall, H.F.; Lassen-Nielsen, A.M.; Nielsen, T.F.; Henriksen, N.H.; Olesen, N.J. Surveillance of health status on eight marine rainbow trout, *Oncorhynchus mykiss* (Walbaum), farms in Denmark in 2006. *J. Fish Dis.* **2008**, *31*, 659–667. [CrossRef]
328. Goldschmidt-Clermont, E.; Hochwartner, O.; Demarta, A.; Caminada, A.P.; Frey, J. Outbreaks of an ulcerative and haemorrhagic disease in Arctic char *Salvelinus alpinus* caused by *Aeromonas salmonicida* subsp. *smithia. Dis. Aquat. Organ.* **2009**, *86*, 81–86. [CrossRef]
329. Varvarigos, P.; Way, K. First isolation and identification of the Infectious Pancreatic Necrosis (IPN) virus from rainbow trout *Onchorhynchus mykiss* fingerlings farmed in Greece. *Bull. Eur. Assoc. Fish Pathol.* **2002**, *22*, 195–200.
330. Athanassopoulou, F.; Billinis, C.; Prapas, T. Important disease conditions of newly cultured species in intensive freshwater farms in Greece: First incidence of nodavirus infection in *Acipenser* sp. *Dis. Aquat. Organ.* **2004**, *60*, 247–252. [CrossRef]
331. Wahli, T.; Burr, S.E.; Pugovkin, D.; Mueller, O.; Frey, J. *Aeromonas sobria*, a causative agent of disease in farmed perch, *Perca fluviatilis* L. *J. Fish Dis.* **2005**, *28*, 141–150. [CrossRef]
332. Edun, O.M. Infectious dropsy of hybrid catfish fingerlings from Nigeria. *J. Anim. Vet. Adv.* **2007**, *6*, 528–529.
333. Leal, Y.; Reyes, M.; Álvarez, J.D.; Obregón, J.; Viña, X. Enteropatogenicidad de bacterias aisladas de peces, del agua y plancton de su entorno en Venezuela. *Rev. Cient. Fac. Ciencias Vet. Univ. Zulia* **2009**, *19*, 446–454.
334. Vineetha, P.; Abraham, T.J. Assessment of fish health problems in freshwater aquaculture systems of Andhra Pradesh, India. *Indian J. Fish.* **2009**, *56*, 335–337.
335. Timur, G.; Timur, M.; Akayli, T.; Korun, J.; Erkan, M. First occurrence of erythrocytic inclusion body syndrome (EIBS) in marine reared rainbow trout (*Oncorhynchus mykiss*) in Turkey. *Isr. J. Aquac.-Bamidgeh* **2011**, *63*, 1–8.
336. Ikpi, G.; Offem, B. Bacterial infection of mudfish *Clarias gariepinus* (Siluriformes: Clariidae) fingerlings in tropical nursery Ponds. *Rev. Biol. Trop.* **2011**, *59*, 751–759. [CrossRef] [PubMed]
337. Pridgeon, J.W.; Klesius, P.H.; Mu, X.; Carter, D.; Fleming, K.; Xu, D.; Srivastava, K.; Reddy, G. Identification of unique DNA sequences present in highly virulent 2009 Alabama isolates of *Aeromonas hydrophila*. *Vet. Microbiol.* **2011**, *152*, 117–125. [CrossRef]
338. Lazăr, M. Epidemiologic, etiologic and lesional aspects of aeromonosis of cyprinids from the hydrographic basin of the Prut river, Romania. *Afr. J. Microbiol. Res.* **2012**, *6*, 1723–1729.
339. Han, J.E.; Kim, J.H.; Choresca, C.H.; Shin, S.P.; Jun, J.W.; Chai, J.Y.; Park, S.C. Prevalence of tet gene and complete genome sequencing of tet gene-encoded plasmid (pAHH01) isolated from *Aeromonas* species in south Korea. *J. Appl. Microbiol.* **2012**, *112*, 631–638. [CrossRef]
340. Zheng, W. Grass carp (*Ctenopharyngodon idellus*) infected with multiple strains of *Aeromonas hydrophila*. *Afr. J. Microbiol. Res.* **2012**, *6*, 4512–4520.
341. Boran, H.; Terzi, E.; Altinok, I.; Capkin, E.; Bascinar, N. Bacterial diseases of cultured Mediterranean horse mackerel (*Trachurus mediterraneus*) in sea cages. *Aquaculture* **2013**, *396–399*, 8–13. [CrossRef]
342. Sharma, P.; Sihag, R.C.; Bhradwaj, A. Isolation and identification of pathogenic bacteria and fungi isolated from skin ulcers of *Cirrhinus mrigala*. *Indian J. Anim. Res.* **2013**, *47*, 283–291.
343. Cagatay, I.T.; Şen, E.B. Detection of pathogenic *Aeromonas hydrophila* from rainbow trout (*Oncorhynchus mykiss*) farms in Turkey. *Int. J. Agric. Biol.* **2014**, *16*, 435–438.
344. Modarres Mousavi Behbahani, S.M.; Akhlaghi, M.; Sharifiyazdi, H. Phenotypic and genetic diversity of motile aeromonads isolated from diseased fish and fish farms. *Iran. J. Vet. Res.* **2014**, *15*, 238–243.

345. Kumar, K.; Prasad, K.P.; Tripathi, G.; Raman, R.P.; Kumar, S.; Tembhurne, M.; Purushothaman, C.S. Isolation, identification, and pathogenicity of a virulent *Aeromonas jandaei* associated with mortality of farmed *Pangasianodon hypophthalmus*, in India. *Isr. J. Aquac.-Bamidgeh* **2015**, *67*, 20727.
346. Gai, C.; Ye, W.; Lu, L.; Li, Y.; Yang, X.; Cao, H. *Aeromonas hydrophila*: A causative agent for tail rot disease in freshwater cultured Murray cod *Maccullochella peelii*. *Isr. J. Aquac.-Bamidgeh* **2016**, *68*, 1–8. [CrossRef]
347. Türe, M.; Alp, H. Identification of bacterial pathogens and determination of their antibacterial resistance profiles in some cultured fish in Turkey. *J. Vet. Res.* **2016**, *60*, 141–146. [CrossRef]
348. Deng, Y.; Wu, Y.; Jiang, L.; Tan, A.; Zhang, R.; Luo, L. Multi-drug resistance mediated by class 1 integrons in *Aeromonas* isolated from farmed freshwater animals. *Front. Microbiol.* **2016**, *7*, 935. [CrossRef]
349. Jawahar Abraham, T.; Sarker, S.; Dash, G.; Patra, A.; Adikesavalu, H. *Chryseobacterium* sp. PLI2 and *Aeromonas hydrophila* co-infection in pacu, *Piaractus brachypomus* (Cuvier, 1817) fries cultured in West Bengal, India. *Aquaculture* **2017**, *473*, 223–227. [CrossRef]
350. Hayakijkosol, O.; Owens, L.; Picard, J. Case report of bacterial infections in a redclaw crayfish (*Cherax quadricarinatus*) hatchery. *Aquaculture* **2017**, *475*, 1–7. [CrossRef]
351. Kayiş, S.; Er, A.; Kangel, P.; Kurtoğlu, I.Z. Bacterial pathogens and health problems of *Acipenser gueldenstaedtii* and *Acipenser baerii* sturgeons reared in the eastern Black Sea region of Turkey. *Iran. J. Vet. Res.* **2017**, *18*, 18–24.
352. Orozova, P.; Sirakov, I.; Austin, D.A.; Austin, B. Recovery of *Bacillus mycoides*, *B. pseudomycoides* and *Aeromonas hydrophila* from common carp (*Cyprinus carpio*) and rainbow trout (*Oncorhynchus mykiss*) with gill disease. *J. Fish Dis.* **2018**, *41*, 125–129. [CrossRef] [PubMed]
353. Perretta, A.; Antúnez, K.; Zunino, P. Phenotypic, molecular and pathological characterization of motile aeromonads isolated from diseased fishes cultured in Uruguay. *J. Fish Dis.* **2018**, *41*, 1559–1569. [CrossRef] [PubMed]
354. Mansour, A.; Mahfouz, N.B.; Husien, M.M.; Omer, A.A.E.Z.M.; Moustafa, E.M. Molecular characterisation and pathogenicity evaluation of *Aeromonas hydrophila* strains isolated from cultured tilapia *Oreochromis niloticus* in Egypt. *Indian J. Fish.* **2019**, *66*, 93–100. [CrossRef]
355. Mokrani, D.; Cerezuela, R.; Oumouna, M.; Esteban, M.Á.; Cuesta, A. Bacteriological, metabolic and immunological evaluation of european sea bass reared in ponds with heated water under a natural vibriosis-like outbreak. *Pak. Vet. J.* **2019**, *39*, 329–334. [CrossRef]
356. Zahran, E.; Ramadan, H.; Almoty, A.M.A.; Abdelkhalek, A.; Hossain, F.M.A. Molecular characterization and antibiotic resistance of pathogenic strains of *Aeromonas* spp. isolated from fish and humans in Egypt and their virulence in Nile tilapia. *Wien. Tierärztliche Mon.* **2019**, *106*, 251–257.
357. Ravi, A.; Das, S.; Basheer, J.; Chandran, A.; Benny, C.; Somaraj, S.; Korattiparambil Sebastian, S.; Mathew, J.; Edayileveettil Krishnankutty, R. Distribution of antibiotic resistance and virulence factors among the bacteria isolated from diseased *Etroplus suratensis*. *3 Biotech.* **2019**, *9*, 138. [CrossRef]
358. Preena, P.G.; Dharmaratnam, A.; Raj, N.S.; Kumar, T.V.A.; Raja, S.A.; Swaminathan, T.R. Antibiotic susceptibility pattern of bacteria isolated from freshwater ornamental fish, guppy showing bacterial disease National Center for Biotechnology Information. *Biologia* **2019**, *74*, 1055–1062. [CrossRef]
359. Gao, T.; Cui, B.; Kong, X.; Bai, Z.; Zhuang, X.; Qian, Z. Investigation of bacterial diversity and pathogen abundances in gibel carp (*Carassius auratus gibelio*) ponds during a cyprinid herpesvirus 2 outbreak. *Microbiologyopen* **2019**, *8*, e907. [CrossRef]
360. Preena, P.G.; Arathi, D.; Raj, N.S.; Arun Kumar, T.V.; Arun Raja, S.; Reshma, R.N.; Raja Swaminathan, T. Diversity of antimicrobial-resistant pathogens from a freshwater ornamental fish farm. *Lett. Appl. Microbiol.* **2020**, *71*, 108–116. [CrossRef]
361. Heiss, C.; Wang, Z.; Thurlow, C.M.; Hossain, M.J.; Sun, D.; Liles, M.R.; Saper, M.A.; Azadi, P. Structure of the capsule and lipopolysaccharide O-antigen from the channel catfish pathogen, *Aeromonas hydrophila*. *Carbohydr. Res.* **2019**, *486*, 107858. [CrossRef]
362. Ranjbar, R.; Salighehzadeh, R.; Sharifiyazdi, H. Antimicrobial resistance and incidence of integrons in *Aeromonas* species isolated from diseased freshwater animals and water samples in Iran. *Antibiotics* **2019**, *8*, 4–10. [CrossRef] [PubMed]
363. Zhao, X.-L.; Jin, Z.-H.; Di, G.-L.; Li, L.; Kong, X.-H. Molecular characteristics, pathogenicity and medication regimen of *Aeromonas hydrophila* isolated from common carp (*Cyprinus carpio* L.). *J. Vet. Med. Sci.* **2019**, *81*, 1769–1775. [CrossRef]
364. Li, X.M.; Zhu, Y.J.; Ringø, E.; Yang, D.G. Prevalence of *Aeromonas hydrophila* and *Pseudomonas fluorescens* and factors influencing them in different freshwater fish ponds. *Iran. J. Fish. Sci.* **2020**, *19*, 111–124.
365. Borella, L.; Salogni, C.; Vitale, N.; Scali, F.; Moretti, V.M.; Pasquali, P.; Alborali, G.L. Motile aeromonads from farmed and wild freshwater fish in northern Italy: An evaluation of antimicrobial activity and multidrug resistance during 2013 and 2016. *Acta Vet. Scand.* **2020**, *62*, 6. [CrossRef] [PubMed]
366. Zhu, W.; Zhou, S.; Chu, W. Comparative proteomic analysis of sensitive and multi-drug resistant *Aeromonas hydrophila* isolated from diseased fish. *Microb. Pathog.* **2020**, *139*, 103930. [CrossRef] [PubMed]
367. Algammal, A.M.; Mohamed, M.F.; Tawfiek, B.A.; Hozzein, W.N.; Kazzaz, W.M.E.; Mabrok, M. Molecular typing, antibiogram and PCR-RFLP based detection of *Aeromonas hydrophila* complex isolated from *Oreochromis niloticus*. *Pathogens* **2020**, *9*, 238. [CrossRef] [PubMed]
368. Sahoo, P.K.; Pattanayak, S.; Paul, A.; Sahoo, M.K.; Kumar, P.R. Carp edema virus in ornamental fish farming in India: A potential threat to koi carps but not to co-cultured Indian major carp or goldfish. *Indian J. Exp. Biol.* **2020**, *58*, 254–262.

369. Nicholson, P.; Mon-on, N.; Jaemwimol, P.; Tattiyapong, P.; Surachetpong, W. Coinfection of tilapia lake virus and *Aeromonas hydrophila* synergistically increased mortality and worsened the disease severity in tilapia (*Oreochromis* spp.). *Aquaculture* **2020**, *520*, 734746. [CrossRef]
370. El-Bahar, H.M.; Ali, N.G.; Aboyadak, I.M.; Khalil, S.A.E.S.; Ibrahim, M.S. Virulence genes contributing to *Aeromonas hydrophila* pathogenicity in *Oreochromis niloticus*. *Int. Microbiol.* **2019**, *22*, 479–490. [CrossRef]
371. Thomas, J.; Madan, N.; Nambi, K.S.N.; Abdul Majeed, S.; Nazeer Basha, A.; Sahul Hameed, A.S. Studies on ulcerative disease caused by *Aeromonas caviae*-like bacterium in Indian catfish, *Clarias batrachus* (Linn). *Aquaculture* **2013**, *376–379*, 146–150. [CrossRef]
372. Mohammed, H.H.; Peatman, E. Winter kill in intensively stocked channel catfish (*Ictalurus punctatus*): Coinfection with *Aeromonas veronii*, *Streptococcus parauberis* and *Shewanella putrefaciens*. *J. Fish Dis.* **2018**, *41*, 1339–1347. [CrossRef]
373. Galeotti, M.; Kazarnikova, A.V.; Shestakovskaya, H.V.; Trishina, A.V.; Turchenko, A.A. Abiotic factors and mixed bacterial infections caused mortality in cage reared Lena sturgeon (*Acipenser baeri*). *Bull. Eur. Assoc. Fish Pathol.* **2015**, *35*, 192–200.
374. Soto-Rodriguez, S.A.; Cabanillas-Ramos, J.; Alcaraz, U.; Gomez-Gil, B.; Romalde, J.L. Identification and virulence of *Aeromonas dhakensis*, *Pseudomonas mosselii* and *Microbacterium paraoxydans* isolated from Nile tilapia, *Oreochromis niloticus*, cultivated in Mexico. *J. Appl. Microbiol.* **2013**, *115*, 654–662. [CrossRef] [PubMed]
375. Uzun, E.; Ogut, H. The isolation frequency of bacterial pathogens from sea bass (*Dicentrarchus labrax*) in the southeastern Black Sea. *Aquaculture* **2015**, *437*, 30–37. [CrossRef]
376. Dong, H.T.; Nguyen, V.V.; Le, H.D.; Sangsuriya, P.; Jitrakorn, S.; Saksmerprome, V.; Senapin, S.; Rodkhum, C. Naturally concurrent infections of bacterial and viral pathogens in disease outbreaks in cultured Nile tilapia (*Oreochromis niloticus*) farms. *Aquaculture* **2015**, *448*, 427–435. [CrossRef]
377. Lü, A.; Song, Y.; Hu, X.; Sun, J.; Li, L.; Pei, C.; Zhang, C.; Nie, G. *Aeromonas veronii*, associated with skin ulcerative syndrome, isolated from the goldfish (*Carassius auratus*) in China. *Isr. J. Aquac.-Bamidgeh* **2016**, *68*, 1–10. [CrossRef]
378. Sun, J.; Zhang, X.; Gao, X.; Jiang, Q.; Wen, Y.; Lin, L. Characterization of virulence properties of *Aeromonas veronii* isolated from diseased gibel carp (*Carassius gibelio*). *Int. J. Mol. Sci.* **2016**, *17*, 496. [CrossRef]
379. Song, Y.; Hu, X.; Lü, A.; Sun, J.; Yiksung, Y.; Pei, C.; Zhang, C.; Li, L. Isolation and characterization of *Aeromonas veronii* from ornamental fish species in China. *Isr. J. Aquac.-Bamidgeh* **2017**, *69*, 21023.
380. Smyrli, M.; Prapas, A.; Rigos, G.; Kokkari, C.; Pavlidis, M.; Katharios, P. *Aeromonas veronii* infection associated with high morbidity and mortality in farmed European seabass *Dicentrarchus labrax* in the Aegean Sea, Greece. *Fish Pathol.* **2017**, *52*, 68–81. [CrossRef]
381. Amal, M.N.A.; Koh, C.B.; Nurliyana, M.; Suhaiba, M.; Nor-Amalina, Z.; Santha, S.; Diyana-Nadhirah, K.P.; Yusof, M.T.; Ina-Salwany, M.Y.; Zamri-Saad, M. A case of natural co-infection of tilapia lake virus and *Aeromonas veronii* in a Malaysian red hybrid tilapia (*Oreochromis niloticus* × *O. mossambicus*) farm experiencing high mortality. *Aquaculture* **2018**, *485*, 12–16. [CrossRef]
382. Gholamhosseini, A.; Taghadosi, V.; Shiry, N.; Akhlaghi, M.; Sharifiyazdi, H.; Soltanian, S.; Ahmadi, N. First isolation and identification of *Aeromonas veronii* and *Chryseobacterium joostei* from reared sturgeons in Fars province, Iran. *Vet. Res. Forum* **2018**, *9*, 113–119. [PubMed]
383. Ramesh, D.; Souissi, S. Antibiotic resistance and virulence traits of bacterial pathogens from infected freshwater fish, *Labeo rohita*. *Microb. Pathog.* **2018**, *116*, 113–119. [CrossRef] [PubMed]
384. Terrazas, M.M.; Anderson, C.L.; Jacobs, S.J.; Cain, K.D. Identification of two pathogenic *Aeromonas* species isolated from juvenile burbot during production-Rrelated epizootics. *J. Aquat. Anim. Health* **2018**, *30*, 201–209. [CrossRef] [PubMed]
385. Lazado, C.C.; Zilberg, D. Pathogenic characteristics of *Aeromonas veronii* isolated from the liver of a diseased guppy (*Poecilia reticulata*). *Lett. Appl. Microbiol.* **2018**, *67*, 476–483. [CrossRef] [PubMed]
386. Xiucai, H.; Xiaoxue, L.; Aijun, L.; Jingfeng, S.; Yajiao, S. Characterization and pathology of *Aeromonas veronii* biovar *sobria* from diseased sheatfish *Silurus glanis* in China. *Isr. J. Aquac.* **2019**, *71*, 1–11.
387. Dworaczek, K.; Drzewiecka, D.; Pękala-Safińska, A.; Turska-Szewczuk, A. Structural and serological studies of the O6-related antigen of *Aeromonas veronii* bv. *sobria* strain K557 isolated from *Cyprinus carpio* on a Polish fish farm, which contains l-perosamine (4-amino-4,6-dideoxy-l-mannose), a unique sugar characteristic for *Aeromonas* serogroup O6. *Mar. Drugs* **2019**, *17*, 399.
388. Xia, L.; Han, P.; Cheng, X.; Li, Y.; Zheng, C.; Yuan, H.; Zhang, W.; Xu, Q. *Aeromonas veronii* caused disease and pathological changes in Asian swamp eel *Monopterus albus*. *Aquac. Res.* **2019**, *50*, 2978–2985. [CrossRef]
389. Raj, N.S.; Swaminathan, T.R.; Dharmaratnam, A.; Raja, S.A.; Ramraj, D.; Lal, K.K. *Aeromonas veronii* caused bilateral exophthalmia and mass mortality in cultured Nile tilapia, *Oreochromis niloticus* (L.) in India. *Aquaculture* **2019**, *512*, 734278. [CrossRef]
390. Smyrli, M.; Triga, A.; Dourala, N.; Varvarigos, P.; Pavlidis, M.; Quoc, V.H.; Katharios, P. Comparative study on a novel pathogen of European seabass. Diversity of *Aeromonas veronii* in the aegean sea. *Microorganisms* **2019**, *17*, 399. [CrossRef]
391. Hoai, T.D.; Trang, T.T.; Van Tuyen, N.; Giang, N.T.H.; Van Van, K. *Aeromonas veronii* caused disease and mortality in channel catfish in Vietnam. *Aquaculture* **2019**, *513*, 734425. [CrossRef]
392. El Latif, A.; Elabd, H.; Amin, A.; Eldeen, A.I.N.; Shaheen, A.A. High mortalities caused by *Aeromonas veronii*: Identification, pathogenicity, and histopathologicalstudies in *Oreochromis niloticus*. *Aquac. Int.* **2019**, *27*, 1725–1737. [CrossRef]
393. ChiHsin, H.; ChongYi, L.; JongKang, L.; ChanShing, L. Control of the eel (*Anguilla japonica*) pathogens, *Aeromonas hydrophila* and *Edwardsiella tarda*, by bacteriophages. *J. Fish. Soc. Taiwan* **2000**, *27*, 21–31.
394. Cao, Y.; Li, S.; Wang, D.; Zhao, J.; Xu, L.; Liu, H.; Lu, T.; Mou, Z. Genomic characterization of a novel virulent phage infecting the *Aeromonas hydrophila* isolated from rainbow trout (*Oncorhynchus mykiss*). *Virus Res.* **2019**, *273*, 197764. [CrossRef] [PubMed]