Fish Vaccines

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Vaccination studies in aquaculture systems are strategically associated with the economically and environmentally sustainable management of aquaculture production worldwide. Historically, most licensed fish vaccines have been developed as inactivated pathogens combined with adjuvants and provided via immersion or injection. In comparison, live vaccines can simulate a whole pathogenic illness and elicit a strong immune response, making them better suited for oral or immersion-based therapy methods to control diseases. Advanced approaches in vaccine development involve targeting specific pathogenic components, including the use of recombinant genes and proteins. Vaccines produced using these techniques, some of which are currently commercially available, appear to elicit and promote higher levels of immunity than conventional fish vaccines. These technological advancements are promising for developing sustainable production processes for commercially important aquatic species.

fish aquaculture bacterial pathogens immunity vaccines

1. Aquaculture Diseases

Infections in fish leading to disease outbreaks are a major concern for the aquaculture sector because they can result in significant economic damage owing to morbidity and death. The high fish-rearing densities currently used in aquaculture enable the transfer and spread of pathogenic microorganisms and are often a primary cause of such catastrophic outbreaks [1]. Intensive farming practices exert huge stresses on cultured aquatic species, compromising their innate immune defenses against various disease-causing bacterial and viral pathogens. Adequate husbandry and overall management, including biosecurity, nutrition genetics, system management, and water quality, are crucial for aquaculture production in all intensive culture farming practices, irrespective of whether individual or several species of fish are produced in dense populations [2]. In China, India, and Vietnam, fish diseases are estimated to contribute to more than 30% of the overall production loss [3]. Several bacterial and viral pathogens and parasites are opportunistic and occur in the environment or as asymptomatic carriers on some fish, which renders aquaculture facilities highly susceptible to disease outbreaks and hinders the development of an efficient, cost-effective, and stable aquaculture process [4]. The appearance and progression of fish disease are determined by the relationship between the pathogen, host, and environment. Stressful conditions, including high population density, change in temperature, and hypoxia, can hasten the spread of pathogenic bacteria and result in major disease outbreaks [5]. Thus, multidisciplinary studies on the characteristics of potential fish pathogens, the biology of the fish hosts, and an adequate understanding of the global environmental factors affecting are important to investigate appropriate measures for the prevention and control of the major diseases limiting fish production in aquaculture.

2. Bacterial Pathogens of Fish

Several bacterial infections in fish species, including Aeromonas septicemia [6], Edwardsiellosis [7], Columnaris [8], Streptococcosis [9], and vibriosis [10] have been reported in the aquaculture sector [11]. Nevertheless, a few of these pathogens are found to be highly responsible for the majority of global economic losses in aquaculture production [12]. Bacterial species responsible for disease outbreaks in different fish species are mentioned in **Table 1**. *Aeromonas* spp. are among the most common types of bacterial pathogens in numerous fish species that occur in freshwater and tropical environments and cause bacterial hemorrhage in cultured fishes [13]. *Aeromonas salmonicida* is one of the oldest known fish pathogens that occurs worldwide in both fresh and marine waters aquaculture regions and is associated with skin ulceration and hemorrhages found as recurrent clinical symptoms of infection [14][15].

Table 1. Bacterial Pathogens of Fishes.

Agents	Disease	Host Fish Targets	References
Aeromonas salmonicida	Furunculosis	trout, salmon, goldfish, koi, and a wide range of fish species	[14][16][17][18]
Aeromonas hydrophila	Motile Aeromonas septicemia (MAS), hemorrhagic septicemia, red-sore disease, ulcer disease, epizootic ulcerative syndrome (EUS)	tilapia, catfish, striped salmonid, non-salmonid fish, sturgeon, bass, and eel	[14][17][18][19]
Edwardsiella ictaluri	Enteric septicemia	Catfish and tilapia	[20][21][22][23]
Edwardsiella tarda	Edwardsiellosis	Salmon, carps, tilapia, catfish, striped bass, flounder, and yellowtail	[24][25][26]
Yersinia ruckeri	Enteric redmouth	Salmonids, eel, minnows, sturgeon, and crustaceans	[27][28][29][30]
Piscirickettsia salmonis	Piscirickettsiosis	Salmonids	[30][31][32][33]
Flavobacterium psychrophilum	Coldwater disease	Salmonids, carp, eel, tench, perch, ayu	[34][35][36]
Flavobacterium columnare	Columnaris disease	cyprinids, salmonids, silurids, eel, and sturgeon	[37][38][39]

Agents	Disease	Host Fish Targets	References
Pseudomonas anguilliseptica	Pseudomonadiasis, winter disease	Sea bream, eel, turbot, and ayu	[40][41][42]
Vibrio anguillarum	Vibriosis	Salmonids, turbot, sea bass, striped bass, eel, ayu, cod, and red sea bream	[10][43][44]
Vibrio salmonicida	Vibriosis	Atlantic salmon, cod	[45][46][47]
Vibrio carchariae	Vibriosis, infectious gastroenteritis	Shark, abalone, red drum, sea bream, sea bass, cobia, and flounder	[48][49][50]
Moritella viscosa	Winter ulcer	Atlantic salmon	[51][52][53]
Tenacibaculum maritimum	Flexibacteriosis	Turbot, salmonids, sole, sea bass, gilthead sea bream, red sea bream, and flounder	[54][55][56]
Lactococcus garvieae	Streptococcosis or lactococcosis	Yellowtail, rainbow trout, and eel	[57][58][59][60]
Streptococcus iniae	Streptococcosis	Adriatic sturgeon, rainbow trout	[61][62][63]
Streptococcus parauberis	Streptococcosis	Turbot	[64][65][66]
Streptococcus phocae	Streptococcosis	Atlantic salmon	[67][68][69]
Mycobacterium marinum	Mycobacteriosis [73]	Sea bass, turbot, and Atlantic salmon	[70][71][72]

pite many treat fish disease, these are associated with obvious disadvantages such as drug resistance and safety concerns of consumers and the environment [74]. Vaccination is an effective technique to prevent a large variety of bacterial and viral infections and contributes to the environmental, social, and economic sustainability of aquaculture production globally [75]. Since the initial reports in the 1940s, several vaccines have been developed that have greatly reduced the impact of loss caused by bacterial and viral infections in fish [76][77]. Millions of fish are currently vaccinated each year, and there has been a shift away from using various antibiotics and toward immunization in different parts of the world [78].

A component either contained in or produced from the fish pathogen is used as an antigen to develop the vaccine [75][79]. This component will be involved in the activation of the innate or adaptive immune responses of the fish in response to a specific microbial infection. Over 100,000 research reports on fish vaccine development have been published in the last two decades, as well as several reviews on the history, developments, types, and routes of administration, and the opportunities and challenges of producing fish vaccines have been studied elaborately [80]. Many studies have summarized the importance of using adjuvants and immunostimulants in boosting the immune response of fish vaccinations, as well as delivery strategies [81][82].

Several inactivated, live-attenuated, and DNA vaccines have been developed and are currently applied in large-scale fish farming operations. The first successful available commercial bacterial vaccine was developed against enteric redmouth disease and vibriosis and was introduced in the United States in the late 1970s. It was developed based on whole-cell inactivation and administrated through immersion methods [83][84]. Since 1990 the global development of fish vaccines has followed a path similar to that of human and veterinary vaccines, with extensive interactions between research and development, pharmaceutical industries, and regulatory bodies of concerned geographical regions. The major fish vaccine producers include Novartis Animal Health (Switzerland), Intervet International (The Netherlands), Pharmaq (Norway), Bayer Animal Health (Bayotek)/Microtek, Inc. (Germany/Canada), and Schering-Plough Animal Health (USA). The global commercial market for these companies is dominated by salmon and trout aquaculture productions [83].

There is a need for a comprehensive assessment of the current state of the fish vaccine sector due to the emergence of new vaccination technology developments. Over 26 licensed fish vaccines are available for use in a different range of fish species worldwide (**Table 2**). Most of the developed vaccines have been licensed for use in a number of aquaculture species by the United States Department of Agriculture (USDA) and are mainly prepared using traditional production methods that involve the cultivation of specific targeted pathogens [85][86]. According to the USDA, vaccines are currently provided to 77 types of fish against more than 22 types of different bacterial and six viral pathogenic specie [87]. Various countries, including Japan and Korea, have licensed and commercialized their fish vaccines [88][89]. In Japan, nine pharmaceutical industries produce fish vaccines for the Japanese market, with 29 vaccine formulations approved since 2018. Vaccines against eight bacterial species and two viral species have been approved and are in use for more than 13 types of fish species [88]. In Korea, 29 vaccines for ten types of fish pathogens are approved and commercially available [89].

Table 2. USDA Approved Bacterial Fish Vaccines.

Disease	Pathogen	Vaccine Type	Delivery Methods	Country/Region	Make
Vibriosis	*Vibrio anguillarum; Vibrio ordalii; Vibrio salmonicida*	Inactivated	IP or IMM	USA, Canada, Japan, Europe, Australia	Merck Animal Health
Furunculosis	*Aeromonas salmonicida,* subsp. *Salmonicida*	Inactivated	IP or IMM	USA, Canada, Chile, Europe, Australia	MSD Animal Health
Bacterial kidney disease (BKD)	*Renibacterium, salmoninarum*	Avirulent live culture	IP	Canada, Chile, USA	Renogen
Enteric septicemia of catfish (ESC)	*Edwarsiella ictaluri*	Inactivated	IP	Vietnam	Pharmaq
Columnaris disease	*Flavobacterium columnaris*	Attenuated	IMM	USA	Merck Animal Health

Disease	Pathogen	Vaccine Type	Delivery Methods	Country/Region	Make
Pasteurellosis	*Pasteurella piscicida*	Inactivated	IMM	USA, Europe, Taiwan, Japan	Pharmaq AS
Lactococcosis	*Lactococcus garvieae*	Attenuated	IP	Spain	hipara
Streptococcus infections	*Streptococcus* spp.	Inactivated	IP	Taiwan Province of China, Japan, Brazil, Indonesia	Aquavac-vaccines
Salmonid rickettsial septicemia	*Piscirickettsia salmonis*	Inactivated	IP	Chile	Pharmaq
Motile Aeromonas septicemia (MAS)	*Aeromonas hydrophila*, *A. caviae*, *A. sobria*	Inactivated	IP	Asia, Europe, United States	Pharmaq
Wound Disease	*Moritella viscosa*	Inactivated	IP	Norway, UK, Ireland, Iceland	Pharmaq
Tenacibaculosis	*Tenacibaculum maritimum*	Inactivated	IP	Spain	hipara
Channel Catfish Septicemia	*Edwardsiella ictaluri*	Avirulent live culture	IMM	United States	AquaVac
Enteric Redmouth Disease	*Yersinia ruckeri*	Attenuated	IMM	United States	Elanco (Aqua Health)

4. Conclusions

Large-scale reductions in the usage of antibiotics were brought on by effective fish vaccinations. But combining all factors that interfere with development to a ministration method remains the real issue in the fish vaccine. Despite several positive results in research and experimental trials with a moderate to high market potential for fish vaccines, there are only a few approved vaccines available on the market to protect against diseases in economically important fish. However, with recent advancements, multiple next-generation vaccine developments can be achieved against various infectious pathogens, especially bacteria, with more clearly defined adjuvants, microcarriers, and nanocarrier-based precisely targeted vaccines to produce higher protective immunity in cultured fish species, which may be available soon for the aquaculture sector. Research on vaccine formulations comprising the most suitable antigenic components, as well as field trial studies that corroborate laboratory findings, will aid in the development of a fish vaccine that is effective against the majority of bacterial infections. This will contribute to

1. Rohani, M.F.; Islam, S.M.; Hossain, M.K.; Ferdous, Z.; Siddik, M.A.; Nuruzzaman, M.; Padeniya, U.; Brown, C.; Shahjahan, M. Probiotics, Prebiotics and Synbiotics Improved the Functionality of Aquafeed: Upgrading Growth, Reproduction, Immunity and Disease Resistance in Fish. Fish Shellfish Immunol. 2022, 120, 569–589.
2. Muktar, Y.; Tesfaye, S. Present Status and Future Prospects of Fish Vaccination: A Review. J. Vet. Sci. Technol. 2016, 7, 1000299.
3. Mohd-Aris, A.; Muhamad-Sofie, M.H.N.; Zamri-Saad, M.; Daud, H.M.; Yasin Ina-Salwany, M. Live Vaccines against Bacterial Fish Diseases: A Review. Vet. World 2019, 12, 1806–1815.
4. Jorgensen, L. von G. Zebrafish as a Model for Fish Diseases in Aquaculture. Pathogens 2020, 9, 609.
5. Hamed, S.B.; Ranzani-Paiva, M.J.T.; Tachibana, L.; de Carla Dias, D.; Ishikawa, C.M.; Esteban, M.A. Fish Pathogen Bacteria: Adhesion, Parameters Influencing Virulence and Interaction with Host Cells. Fish Shellfish Immunol. 2018, 80, 550–562.

the sustainable growth of the economy and control the impact of environmental pollution caused by conventional antibiotics and chemical-based treatments.

6. Thirumalaikumar, E.; Lelin, C.; Sathishkumar, R.; Vimal, S.; Anand, S.B.; Babu, M.M.; Citarasu, T. Oral Delivery of PVAX-OMP and PVAX-Hly DNA Vaccine Using Chitosan-Tripolyphosphate (Cs-TPP) Nanoparticles in Rohu, (Labeo rohita) for Protection against Aeromonas Hydrophila Infection. Fish Shellfish Immunol. 2021, 115, 189–197.
7. Buján, N.; Toranzo, A.E.; Magariños, B. Edwardsiella piscicida: A Significant Bacterial Pathogen of Cultured Fish. Dis. Aquat. Org. 2018, 131, 59–71.
8. Declercq, A.M.; Haesebrouck, F.; van den Broeck, W.; Bossier, P.; Decostere, A. Columnaris Disease in Fish: A Review with Emphasis on Bacterium-Host Interactions. Vet. Res. 2013, 44, 27.
9. Luo, X.; Fu, X.; Liao, G.; Chang, O.; Huang, Z.; Li, N. Isolation, Pathogenicity and Characterization of a Novel Bacterial Pathogen Streptococcus Uberis from Diseased Mandarin Fish Siniperca chuatsi. Microb. Pathog. 2017, 107, 380–389.
10. Ji, Q.; Wang, S.; Ma, J.; Liu, Q. A Review: Progress in the Development of Fish Vibrio Spp. Vaccines. Immunol. Lett. 2020, 226, 46–54.
11. Bhatnagar, A.; Kumari, S.; Tyor, A.K. Assessment of Bactericidal Role of Epidermal Mucus of Heteropneustes fossilis and Clarias batrachus (Asian Cat Fishes) against Pathogenic Microbial Strains. Aquac. Fish. 2022, 8, 50–58.
12. Maldonado-Miranda, J.J.; Castillo-Pérez, L.J.; Ponce-Hernández, A.; Carranza-Álvarez, C. Summary of economic losses due to bacterial pathogens in aquaculture industry. Bact. Fish Dis. 2022, 399–417.
13. Ramesh, D.; Souissi, S. Antibiotic Resistance and Virulence Traits of Bacterial Pathogens from Infected Freshwater Fish, Labeo rohita. Microb. Pathog. 2018, 116, 113–119.
14. Menanteau-Ledouble, S.; Kumar, G.; Saleh, M.; El-Matbouli, M. Aeromonas salmonicida: Updates on an Old Acquaintance. Dis. Aquat. Org. 2016, 120, 49–68.
15. Håstein, T.; Hjeltnes, B.; Lillehaug, A.; Skåre, J.U.; Berntssen, M.; Lundebye, A.K. Food Safety Hazards That Occur during the Production Stage: Challenges for Fish Farming and the Fishing Industry. Rev. Sci. Tech. 2006, 25, 607–625.
16. Alghabshi, A.; Austin, B.; Crumlish, M. Aeromonas salmonicida Isolated from Wild and Farmed Fish and Invertebrates in Oman. Int. Aquat. Res. 2018, 10, 145–152.
17. Han, H.J.; Kim, D.Y.; Kim, W.S.; Kim, C.S.; Jung, S.J.; Oh, M.J.; Kim, D.H. Atypical Aeromonas salmonicida Infection in the Black Rockfish, Sebastes schlegeli Hilgendorf, in Korea. J. Fish Dis. 2011, 34, 47–55.
18. Beaz-Hidalgo, R.; Figueras, M.J. Aeromonas Spp. Whole Genomes and Virulence Factors Implicated in Fish Disease. J. Fish Dis. 2013, 36, 371–388.

19. 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.
20. Dong, H.T.; Senapin, S.; Jeamkunakorn, C.; Nguyen, V.V.; Nguyen, N.T.; Rodkhum, C.; Khunrae, P.; Rattanarojpong, T. Natural Occurrence of Edwardsiellosis Caused by Edwardsiella ictaluri in Farmed Hybrid Red Tilapia (Oreochromis Sp.) in Southeast Asia. Aquaculture 2019, 499, 17–23.
21. Kordon, A.O.; Abdelhamed, H.; Karsi, A.; Pinchuk, L.M. Adaptive Immune Responses in Channel Catfish Exposed to Edwardsiella ictaluri Live Attenuated Vaccine and Wild Type Strains through the Specific Gene Expression Profiles. Dev. Comp. Immunol. 2021, 116, 103950.
22. Phuoc, N.N.; Richards, R.; Crumlish, M. Environmental Conditions Influence Susceptibility of Striped Catfish Pangasianodon hypophthalmus (Sauvage) to Edwardsiella ictaluri. Aquaculture 2020, 523, 735226.
23. Li, H.; Zhang, L.; Yu, Y.; Ai, T.; Zhang, Y.; Su, J. Rapid Detection of Edwardsiella ictaluri in Yellow Catfish (Pelteobagrus fulvidraco) by Real-Time RPA and RPA-LFD. Aquaculture 2022, 552, 737976.
24. Xu, T.; Zhang, X.-H. Edwardsiella tarda: An Intriguing Problem in Aquaculture. Aquaculture 2014, 431, 129–135.
25. Pandey, V.; Bhat, R.A.H.; Chandra, S.; Tandel, R.S.; Dubey, M.K.; Sharma, P.; Gehlot, B.; Dash, P.; Joshi, R. Clinical Signs, Lethal Dose and Histopathological Lesions in Grass Carp, Ctenopharyngodon idella Experimentally Infected with Edwardsiella tarda. Microb. Pathog. 2021, 161, 105292.
26. McDermott, C.; Palmeiro, B. Updates on Selected Emerging Infectious Diseases of Ornamental Fish. Vet. Clin. North Am. Exot. Anim. Pract. 2020, 23, 413–428.
27. Ohtani, M.; Villumsen, K.R.; Strøm, H.K.; Lauritsen, A.H.; Aalbæk, B.; Dalsgaard, I.; Nowak, B.; Raida, M.K.; Bojesen, A.M. Effects of Fish Size and Route of Infection on Virulence of a Danish Yersinia ruckeri O1 Biotype 2 Strain in Rainbow Trout (Oncorhynchus mykiss). Aquaculture 2019, 503, 519–526.
28. Acuña, L.G.; Barros, M.J.; Montt, F.; Peñaloza, D.; Núñez, P.; Valdés, I.; Gil, F.; Fuentes, J.A.; Calderón, I.L. Participation of Two SRNA RyhB Homologs from the Fish Pathogen Yersinia ruckeri in Bacterial Physiology. Microbiol. Res. 2021, 242, 126629.
29. Lewin, A.S.; Haugen, T.; Netzer, R.; Tøndervik, A.; Dahle, S.W.; Hageskal, G. Multiplex Droplet Digital PCR Assay for Detection of Flavobacterium psychrophilum and Yersinia ruckeri in Norwegian Aquaculture. J. Microbiol. Methods 2020, 177, 106044.

30. Jozwick, A.K.S.; LaPatra, S.E.; Graf, J.; Welch, T.J. Flagellar Regulation Mediated by the Rcs Pathway Is Required for Virulence in the Fish Pathogen Yersinia ruckeri. Fish Shellfish Immunol. 2019, 91, 306–314.

31. Chettri, J.K.; Al-Jubury, A.; Hansen, M.B.; Lihme, A.; Dalsgaard, I.; Buchmann, K.; Heegaard, P.M.H. Protective Effect of In-Feed Specific IgM towards Yersinia ruckeri in Rainbow Trout. Fish Shellfish Immunol. 2019, 93, 934–939.

32. Marshall, S.H.; Conejeros, P.; Zahr, M.; Olivares, J.; Gómez, F.; Cataldo, P.; Henríquez, V. Immunological Characterization of a Bacterial Protein Isolated from Salmonid Fish Naturally Infected with Piscirickettsia salmonis. Vaccine 2007, 25, 2095–2102.

33. Labra, Á.; Arredondo-Zelada, O.; Flores-Herrera, P.; Marshall, S.H.; Gómez, F.A. In Sílico Identification and Characterization of Putative Dot/Icm Secreted Virulence Effectors in the Fish Pathogen Piscirickettsia salmonis. Microb. Pathog. 2016, 92, 11–18.

34. Starliper, C.E. Bacterial Coldwater Disease of Fishes Caused by Flavobacterium psychrophilum. J. Adv. Res. 2011, 2, 97–108.

35. Viel, A.; Rostang, A.; Morvan, M.L.; Fournel, C.; Daniel, P.; Thorin, C.; Baron, S.; Sanders, P.; Calvez, S. Population Pharmacokinetics/Pharmacodynamics Modelling of Enrofloxacin for the Three Major Trout Pathogens Aeromonas salmonicida, Flavobacterium psychrophilum and Yersinia ruckeri. Aquaculture 2021, 545, 737119.

36. Orieux, N.; Douet, D.G.; Le Hénaff, M.; Bourdineaud, J.P. Prevalence of Flavobacterium psychrophilum Bacterial Cells in Farmed Rainbow Trout: Characterization of Metallothionein A and Interleukin1-β Genes as Markers Overexpressed in Spleen and Kidney of Diseased Fish. Vet. Microbiol. 2013, 162, 127–135.

37. LaFrentz, B.R.; Králová, S.; Burbick, C.R.; Alexander, T.L.; Phillips, C.W.; Griffin, M.J.; Waldbieser, G.C.; García, J.C.; de Alexandre Sebastião, F.; Soto, E.; et al. The Fish Pathogen Flavobacterium columnare Represents Four Distinct Species: Flavobacterium columnare, Flavobacterium covae Sp. Nov., Flavobacterium davisii Sp. Nov. and Flavobacterium oreochromis Sp. Nov., and Emended Description of Flavobacterium columnare. Syst. Appl. Microbiol. 2022, 45, 126293.

38. Ponpukdee, N.; Wangman, P.; Rodkhum, C.; Pengsuk, C.; Chaivisuthangkura, P.; Sithigorngul, P.; Longyant, S. Detection and Identification of a Fish Pathogen Flavobacterium columnare Using Specific Monoclonal Antibodies. Aquaculture 2021, 545, 737231.

39. Singh, S.; Mallik, S.K.; Kala, K.; Shahi, N.; Pathak, R.; Giri, A.K.; Chandra, S.; Pant, K.; Patiyal, R.S. Characterization of Flavobacterium columnare from Farmed Infected Rainbow Trout, Oncorhynchus mykiss (Walbaum, 1792) of Central Indian Himalayan Region, India. Aquaculture 2021, 544, 737118.

40. Fadel, A.; Mabrok, M.; Aly, S. Epizootics of Pseudomonas anguilliseptica among Cultured Seabream (Sparus aurata) Populations: Control and Treatment Strategies. Microb. Pathog. 2018, 121, 1–8.
41. López-Romalde, S.; Magariños, B.; Ravelo, C.; Toranzo, A.E.; Romalde, J.L. Existence of Two O-Serotypes in the Fish Pathogen Pseudomonas anguilliseptica. Vet. Microbiol. 2003, 94, 325–333.
42. Doménech, A.; Fernández-Garayzábal, J.F.; Lawson, P.; García, J.A.; Cutuli, M.T.; Blanco, M.; Gibello, A.; Moreno, M.A.; Collins, M.D.; Domínguez, L. Winter Disease Outbreak in Sea-Bream (Sparus aurata) Associated with Pseudomonas anguilliseptica Infection. Aquaculture 1997, 156, 317–326.
43. Yang, N.; Song, F.; Polyak, S.W.; Liu, J. Actinonin Resistance of Pathogenic Vibrio anguillarum in Aquaculture. Aquaculture 2021, 541, 736850.
44. Zhang, J.; Hu, Y.; Sun, Q.; Li, X.; Sun, L. An Inactivated Bivalent Vaccine Effectively Protects Turbot (Scophthalmus maximus) against Vibrio anguillarum and Vibrio harveyi Infection. Aquaculture 2021, 544, 737158.
45. Bjelland, A.M.; Johansen, R.; Brudal, E.; Hansen, H.; Winther-Larsen, H.C.; Sørum, H. Vibrio salmonicida Pathogenesis Analyzed by Experimental Challenge of Atlantic Salmon (Salmo salar). Microb. Pathog. 2012, 52, 77–84.
46. Bøgwald, J.; Hoffman, J. Structural Studies of the O-Antigenic Oligosaccharide from Vibrio salmonicida Strain C2 Isolated from Atlantic Cod, Gadus morhua L. Carbohydr. Res. 2006, 341, 1965–1968.
47. Karlsen, C.; Paulsen, S.M.; Tunsjø, H.S.; Krinner, S.; Sørum, H.; Haugen, P.; Willassen, N.P. Motility and Flagellin Gene Expression in the Fish Pathogen Vibrio salmonicida: Effects of Salinity and Temperature. Microb. Pathog. 2008, 45, 258–264.
48. Harikrishnan, R.; Balasundaram, C.; Heo, M.S. Influence of Diet Enriched with Green Tea on Innate Humoral and Cellular Immune Response of Kelp Grouper (Epinephelus bruneus) to Vibrio carchariae Infection. Fish Shellfish Immunol. 2011, 30, 972–979.
49. Kim, J.S.; Harikrishnan, R.; Kim, M.C.; Jang, I.S.; Kim, D.H.; Hong, S.H.; Balasundaram, C.; Heo, M.S. Enhancement of Eriobotrya japonica Extracts on Non-Specific Immune Response and Disease Resistance in Kelp Grouper Epinephelus bruneus against Vibrio carchariae. Fish Shellfish Immunol. 2011, 31, 1193–1200.
50. Suginta, W.; Vongsuwan, A.; Songsiriritthigul, C.; Prinz, H.; Estibeiro, P.; Duncan, R.R.; Svasti, J.; Fothergill-Gilmore, L.A. An Endochitinase A from Vibrio carchariae: Cloning, Expression, Mass and Sequence Analyses, and Chitin Hydrolysis. Arch. Biochem. Biophys. 2004, 424, 171–180.
51. MacKinnon, B.; Groman, D.; Fast, M.D.; Manning, A.J.; Jones, P.; MacKinnon, A.M.; St-Hilaire, S. Transmission Experiment in Atlantic Salmon (Salmo salar) with an Atlantic Canadian Isolate of

Moritella viscosa. Aquaculture 2020, 516, 734547.

52. Karlsen, C.; Thorarinsson, R.; Wallace, C.; Salonius, K.; Midtlyng, P.J. Atlantic Salmon Winter-Ulcer Disease: Combining Mortality and Skin Ulcer Development as Clinical Efficacy Criteria against Moritella viscosa Infection. Aquaculture 2017, 473, 538–544.
53. Einarsdottir, T.; Sigurdardottir, H.; Einarsdottir, E.; Bjornsdottir, T.S. Moritella viscosa in Lumpfish (Cyclopterus lumpus) and Atlantic Salmon (Salmo salar). Fish Shellfish Immunol. 2019, 91, 469.
54. Brosnahan, C.L.; Georgiades, E.; McDonald, C.; Keeling, S.E.; Munday, J.S.; Jones, B. Optimisation and Validation of a PCR to Detect Viable Tenacibaculum maritimum in Salmon Skin Tissue Samples. J. Microbiol. Methods 2019, 159, 186–193.
55. Fernández-Álvarez, C.; González, S.F.; Santos, Y. Quantitative PCR Coupled with Melting Curve Analysis for Rapid Detection and Quantification of Tenacibaculum maritimum in Fish and Environmental Samples. Aquaculture 2019, 498, 289–296.
56. Småge, S.B.; Frisch, K.; Brevik, Ø.J.; Watanabe, K.; Nylund, A. First Isolation, Identification and Characterisation of Tenacibaculum maritimum in Norway, Isolated from Diseased Farmed Sea Lice Cleaner Fish Cyclopterus lumpus L. Aquaculture 2016, 464, 178–184.
57. Shahi, N.; Mallik, S.K. Emerging Bacterial Fish Pathogen Lactococcus garvieae RTCLI04, Isolated from Rainbow Trout (Oncorhynchus mykiss): Genomic Features and Comparative Genomics. Microb. Pathog. 2020, 147, 104368.
58. Torres-Corral, Y.; Santos, Y. Clonality of Lactococcus garvieae Isolated from Rainbow Trout Cultured in Spain: A Molecular, Immunological, and Proteomic Approach. Aquaculture 2021, 545, 737190.
59. Patel, P.; Patel, B.; Amaresan, N.; Joshi, B.; Shah, R.; Krishnamurthy, R. Isolation and Characterization of Lactococcus garvieae from the Fish Gut for in Vitro Fermentation with Carbohydrates from Agro-Industrial Waste. Biotechnol. Rep. 2020, 28, e00555.
60. Shahin, K.; Veek, T.; Heckman, T.I.; Littman, E.; Mukkatira, K.; Adkison, M.; Welch, T.J.; Imai, D.M.; Pastenkos, G.; Camus, A.; et al. Isolation and Characterization of Lactococcus garvieae from Rainbow Trout, Onchorhyncus mykiss, from California, USA. Transbound. Emerg. Dis. 2022, 69, 2326–2343.
61. Colussi, S.; Pastorino, P.; Mugetti, D.; Antuofermo, E.; Sciuto, S.; Esposito, G.; Polinas, M.; Tomasoni, M.; Burrai, G.P.; Fernández-Garayzábal, J.F.; et al. Isolation and Genetic Characterization of Streptococcus iniae Virulence Factors in Adriatic Sturgeon (Acipenser naccarii). Microorganisms 2022, 10, 883.
62. Mugetti, D.; Colussi, S.; Pastorino, P.; Varello, K.; Tomasoni, M.; Menconi, V.; Pedron, C.; Bozzetta, E.; Acutis, P.L.; Prearo, M. Episode of Mortality Associated with Isolation of

Streptococcus iniae in Adriatic Sturgeon (Acipenser naccarii Bonaparte, 1836) Reared in Northern Italy. J. Fish Dis. 2022, 45, 939–942.

63. Rashidian, G.; Mahboub, H.H.; Fahim, A.; Hefny, A.A.; Prokić, M.D.; Rainis, S.; Boldaji, J.T.; Faggio, C. Mooseer (Allium hirtifolium) Boosts Growth, General Health Status, and Resistance of Rainbow Trout (Oncorhynchus mykiss) against Streptococcus iniae Infection. Fish Shellfish Immunol. 2022, 120, 360–368.
64. Haines, A.N.; Gauthier, D.T.; Nebergall, E.E.; Cole, S.D.; Nguyen, K.M.; Rhodes, M.W.; Vogelbein, W.K. First Report of Streptococcus parauberis in Wild Finfish from North America. Vet. Microbiol. 2013, 166, 270–275.
65. Gao, Y.; Liu, Y.; Wang, P.; Mo, Z.; Li, J.; Liu, S.; Li, G.; Zhu, M. Isolation, Identification and Vaccine Development of Serotype III Streptococcus parauberis in Turbot (Scophthalmus maximus) in China. Aquaculture 2021, 538, 736525.
66. Jayathilaka, E.H.T.T.; Liyanage, T.D.; Rajapaksha, D.C.; Dananjaya, S.H.S.; Nikapitiya, C.; Whang, I.; de Zoysa, M. Octominin: An Antibacterial and Anti-Biofilm Peptide for Controlling the Multidrug Resistance and Pathogenic Streptococcus parauberis. Fish Shellfish Immunol. 2021, 110, 23–34.
67. Nikolaisen, N.K.; Lindegaard, M.; Lyhs, U.; Strube, M.L.; Hansen, M.S.; Struve, T.; Chriél, M.; Jensen, L.B.; Pedersen, K. First Finding of Streptococcus phocae Infections in Mink (Neovison vison). Res. Vet. Sci. 2021, 139, 145–151.
68. Bethke, J.; Avendaño-Herrera, R. Comparative Genome Analysis of Two Streptococcus phocae Subspecies Provides Novel Insights into Pathogenicity. Mar. Genom. 2017, 31, 53–61.
69. Salazar, S.; Oliver, C.; Yáñez, A.J.; Avendaño-Herrera, R. Comparative Analysis of Innate Immune Responses to Streptococcus phocae Strains in Atlantic Salmon (Salmo salar) and Rainbow Trout (Oncorhynchus mykiss). Fish Shellfish Immunol. 2016, 51, 97–103.
70. Harjula, S.K.E.; Saralahti, A.K.; Ojanen, M.J.T.; Rantapero, T.; Uusi-Mäkelä, M.I.E.; Nykter, M.; Lohi, O.; Parikka, M.; Rämet, M. Characterization of Immune Response against Mycobacterium marinum Infection in the Main Hematopoietic Organ of Adult Zebrafish (Danio rerio). Dev. Comp. Immunol. 2020, 103, 103523.
71. Nakamura, S.I.; Yasuda, M.; Ozaki, K.; Tsukahara, T. Eosinophilic Leukaemia and Systemic Mycobacterium marinum Infection in an African Pygmy Hedgehog (Atelerix albiventris). J. Comp. Pathol. 2020, 181, 33–37.
72. Davidovich, N.; Pretto, T.; Sharon, G.; Zilberg, D.; Blum, S.E.; Baider, Z.; Edery, N.; Morick, D.; Grossman, R.; Kaidar-Shwartz, H.; et al. Cutaneous Appearance of Mycobacteriosis Caused by Mycobacterium marinum, Affecting Gilthead Seabream (Sparus aurata) Cultured in Recirculating Aquaculture Systems. Aquaculture 2020, 528, 735507.

73. Rodger, H.D. Fish Disease Causing Economic Impact in Global Aquaculture. In Fish Vaccines; Birkhäuser Advances in Infectious Diseases; Springer: Berlin/Heidelberg, Germany, 2016; pp. 1–34.
74. Manyi-Loh, C.; Mamphweli, S.; Meyer, E.; Okoh, A. Antibiotic Use in Agriculture and Its Consequential Resistance in Environmental Sources: Potential Public Health Implications. Molecules 2018, 23, 795.
75. 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.
76. Duff, D.C.B. The Oral Immunization of Trout against Bacterium salmonicida. J. Immunol. 1942, 44, 87–94.
77. van Muiswinkel, W.B. A History of Fish Immunology and Vaccination I. The Early Days. Fish Shellfish Immunol. 2008, 25, 397–408.
78. Midtlyng, P.J. Current Use and Need for New Fish Vaccines. Princ. Fish Immunol. 2022, 599–608.
79. Mondal, H.; Thomas, J. A Review on the Recent Advances and Application of Vaccines against Fish Pathogens in Aquaculture. Aquac. Int. 2022, 30, 1971–2000.
80. Adams, A. Progress, Challenges and Opportunities in Fish Vaccine Development. Fish Shellfish Immunol. 2019, 90, 210–214.
81. Raman, R.P.; Kumar, S. Adjuvants for Fish Vaccines. In Fish Immune System and Vaccines; Springer: Singapore, 2022; pp. 231–244.
82. Munang'andu, H.M.; Salinas, I.; Tafalla, C.; Dalmo, R.A. Editorial: Vaccines and Immunostimulants for Finfish. Front. Immunol. 2020, 11, 52312.
83. Sommerset, I.; Krossøy, B.; Biering, E.; Frost, P. Vaccines for Fish in Aquaculture. Expert Rev. Vaccines 2005, 4, 89–101.
84. Gudding, R.; Lillehaug, A.; Evensen, Ø. Recent Developments in Fish Vaccinology. Vet. Immunol. Immunopathol. 1999, 72, 203–212.
85. Bøgwald, J.; Dalmo, R.A. Review on Immersion Vaccines for Fish: An Update 2019. Microorganisms 2019, 7, 627.
86. Hossain, S.; Shefat, T. Vaccines for Use in Finfish Aquaculture. Acta Sci. Pharm. Sci. 2018, 2, 15–19.
87. Tizard, I.R. Fish Vaccines. In Vaccines for Veterinarians; Elsevier: Amsterdam, The Netherlands, 2021; pp. 281–292.e1.
88. Matsuura, Y.; Terashima, S.; Takano, T.; Matsuyama, T. Current Status of Fish Vaccines in Japan. Fish Shellfish Immunol. 2019, 95, 236–247.

89. Hwang, J.Y.; Kwon, M.G.; Seo, J.S.; Hwang, S.D.; Jeong, J.M.; Lee, J.H.; Jeong, A.R.; Jee, B.Y. Current Use and Management of Commercial Fish Vaccines in Korea. Fish Shellfish Immunol. 2020, 102, 20–27.