State-of-the-Art Vaccine for Aquaculture Use

Subjects: Zoology | Biotechnology & Applied Microbiology | Physiology
Contributor: Andrea Miccoli

Infectious diseases caused by bacteria, viruses, or parasites are the major causes of mortality and economic losses in commercial aquaculture. Some pathologies, especially those of bacterial origin, can be treated with commercially available drugs, while others are poorly managed. In fact, despite having been recognized as a useful preventive measure, no effective vaccination against many economically relevant diseases exist yet, such as for viral and parasitic infections.

Keywords: adjuvants ; aquaculture ; experimental challenge ; fish immunology ; fish welfare ; vaccines ; infectious diseases

1. Introduction

Aquaculture has experienced an enormous growth in productive terms, accounting to >527% in the 1990–2018 time frame. In 2018, aquaculture contributed to approximately 46% of the global total production of aquatic organisms (179 M tons) and 52% of seafood for human consumption (fish, crustaceans, mollusks, and other aquatic animals, excluding aquatic mammals, reptiles, seaweeds, and other aquatic plants) [1]. Capture-wise, any further increment in global productions will have to strictly ensure the preservation of natural resources, the 59.6% of which is currently being maximally sustainably fished, and avoid overfishing practices, also because of the severe ecological problems they are linked to (e.g., damages to coastal and marine ecosystems, alteration of multiple trophic levels, and algal blooms) [2][3]. Because of the increasing world population and per capita consumption [4], aquaculture is expected to continue growing, with conservative projections estimating 186 M tons production by year 2030 [5].

Commercial aquaculture is impacted by infectious diseases caused primarily by bacteria, viruses, parasites, and, to a lesser extent, fungi. Bacterial diseases can inflict significant biological, thus economic losses [6][7][8]. While these are usually controllable with antibiotics, the indiscriminate use of these pharmaceuticals is ultimately a threat to human health because of the development and transfer of resistance mechanisms among bacterial species, some of which are also human pathogens. Their employment is therefore strongly regulated in many countries [9].

Various prevention strategies are currently used such as (i) biocontainment measures (e.g., quarantine and disease screening of newly introduced fishes) [10], (ii) water treatment systems (e.g., magnetic, ultraviolet, and ozone sterilization, all practically applicable only in recirculating systems) [11][12], and (iii) probiotics/prebiotics supplementation for immune system stimulation and growth promotion [13].

Fish vaccination can prevent or mitigate disease spreading with proven effectiveness against many relevant pathogens. The vaccine against enteric redmouth disease (caused by *Yersinia ruckeri*) developed in 1970s was the first to become commercially available [14], later followed by vaccines against cold water vibriosis (caused by *Aliivibrio salmonicida*) [15]. Since then, various vaccines have been developed, commercialized, successfully employed and reviewed [16][17]. Still, because of their high development and production costs and general lower efficacy than bacterins, few vaccines exist against viral diseases, and no commercial vaccines at all are available to date against parasitic diseases [18].

2. The factors affecting the efficacy of vaccines

This entry discusses the most promising and updated state-of-the-art vaccine research on three economically relevant aquaculture commodities chosen because of their distinct biological traits and geographical distribution as well as for being representative of different culture systems: European sea bass (*Dicentrarchus labrax*), Nile tilapia (*Oreochromis niloticus*), and Atlantic salmon (*Salmo salar*). From here on, the term “vaccine” is used to describe any substance used to stimulate the immune response or protect fish from pathogens, regardless of their classification (i.e., bacterial, viral, and parasitic). A compilation of mainly experimental formulations against bacterial, viral and parasitic infections is presented for each species (Tables 1–3; Figures 1–3). Commercial vaccines were considered only in particular cases (e.g., when a

commercial product was adjuvanted with a recombinant molecule, when the study was of particular interest because of its large scale or analytical methods, or when commercial and experimental vaccines were compared). Because it is quite difficult to determine the exact variables affecting vaccine efficacy [19], multiple factors such as (i) antigen dose, exposure and uptake, (ii) boost immunization strategy, (iii) adjuvant inclusion, type and performance, (iv) water temperature, (v) fish size, (vi) type, virulence, and route of experimental challenge need to be considered prior to being able to extrapolate fundamental scientific observations. For this reason, we herein provide readers with the essential procedural elements and findings from the available literature with the aim of delivering the most comprehensive understanding on the features and performances of protective vaccines and immunostimulants/adjuvants and, ultimately, on the fish immune response, a crucial end-point for further science-based vaccine developments.

Table 1. Literature regarding experimental and commercial vaccines presented and discussed for European sea bass *Dicentrarchus labrax*. Approximate size refers to the fish body weight (BW) at the time of challenge or relative percentage of survival (RPS) calculation, as stated in or inferred from references. In case of commercial vaccines, the product description was linked. Challenges must be intended as homologous except when stated otherwise. List of abbreviations: ECPs—extracellular products; LPS—lipopolysaccharide; rTNFα—recombinant tumor necrosis factor alpha.

Pathogen	Vaccine Status	Adjuvant	Approx. Size (g)	Challenge	Ref.
Mycobacterium marinum	Experimental	Montanide™ ISA 760 VG	50	Yes	[20]
M. marinum	Experimental	No	20	Yes	[21]
Tenacibaculum maritimum	Experimental	No	30	Yes	[22]
T. maritimum	Experimental	No	5	No	[23]
Vibrio anguillarum + *Vibrio ordalii*	Commercial (AquaVac Vibrio Oral)	rTNFα	30	Yes	[24]
V. anguillarum + *Photobacterium damselae*	Commercial (AlphaJect 2000™ and AquaVac™ Vibrio-Pasteurella)	Non-mineral	35	Yes	[25]
Betanodavirus	Experimental	No	2 and 6	Yes (only one exp. group)	[26]
Betanodavirus	Experimental	No	11	Yes	[27]
Betanodavirus	Experimental	No	6	Yes	[28]
Betanodavirus	Experimental	No	11	Yes	[29]
Betanodavirus	Experimental	No	30	Yes	[30]
Betanodavirus	Experimental	No	6	Yes	[31]

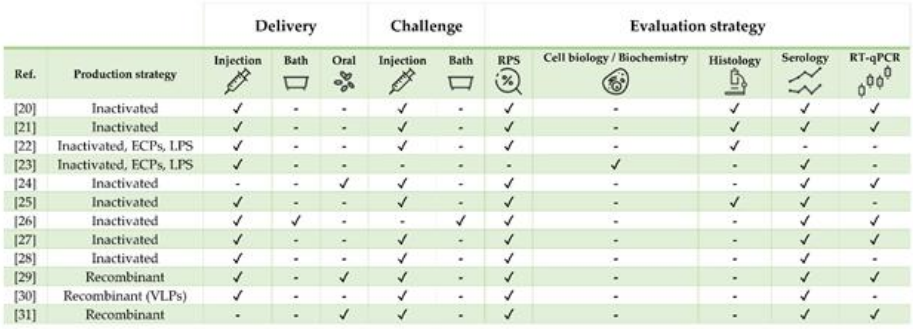

Figure 1. Strategies for vaccine development, administration, and evaluation applied by referenced studies on European sea bass *Dicentrarchus labrax*.

Table 2. Literature regarding experimental and commercial vaccines herein presented and discussed for Nile tilapia *Oreochromis niloticus*. Approximate size refers to the fish BW at the time of challenge or RPS calculation, as stated in or inferred from references. In case of commercial vaccines, the product description was linked. Challenges must be intended as homologous except when stated otherwise.

Pathogen	Vaccine Status	Adjuvant	Approx. Size (g)	Challenge	Ref.
Streptococcus iniae	Experimental	No	10	Yes (homologous and heterologous)	[32]
S. iniae	Experimental	No	40	Yes	[33]
S. iniae	Experimental	No	5	Yes (heterologous)	[34]
S. iniae	Experimental	Oralject™	13	Yes	[35]
S. iniae	Experimental	No	25	Yes	[36]
S. iniae	Experimental	No	3 and 16	Yes	[37]
Streptococcus agalactiae	Experimental	No	100	Yes	[38]
S. agalactiae	Experimental	No	30	Yes (heterologous)	[39]
S. agalactiae	Experimental	No	30	Yes	[40]
Polyvalent (*S. agalactiae*, *S. iniae*, *Lactococcus garvieae* and *Enterococcus faecalis*)	Commercial (Mevac Aquastrept)	Montanide™ IMS 1312 VG	500 and 1-month-old fry	Yes	[41]
Francisella orientalis	Experimental	Montanide™ ISA 736A VG	10	Yes	[42]

F. orientalis	Experimental	Montanide™ (oil-based)	15	Yes (heterologous)	[43]
F. orientalis	Experimental	Montanide™ ISA 736A VG	35	Yes	[44]
Aeromonas hydrophila	Experimental	No	55	Yes	[45]
A. Hydrophila	Experimental	No	10	Yes	[46]
Flavobacterium columnare	Experimental	No	9	Yes (heterologous)	[47]
Vibrio anguillarum	Experimental	No	3.5	Yes	[48]
Edwardsiella tarda	Experimental	Montanide™ ISA 763A VG	102	Yes	[49]
E. tarda	Experimental	No	42	Yes	[50]
Caligus rogercresseyi	Experimental	Montanide™ 888 VG	80	No	[51]

		Delivery			Challenge		Evaluation strategy					
Ref.	Production strategy	Injection	Bath	Oral	Injection	Bath	RPS	Cell biology / Biochemistry	Histology	Pathogen count	Serology	RT-qPCR
[32]	Attenuated	✓	✓	-	✓	-	✓	-	-	-	✓	-
[33]	Attenuated	✓	-	-	✓	-	✓	-	-	-	-	-
[34]	Inactivated	✓	-	-	✓	-	✓	✓	-	-	-	-
[35]	Inactivated	✓	-	✓	✓	-	✓	-	-	-	-	-
[36]	Recombinant	✓	-	-	✓	-	✓	-	-	-	✓	✓
[37]	Inactivated	✓	-	-	✓	-	✓	-	-	-	✓	-
[38]	Recombinant	-	-	✓	✓	-	✓	-	✓	-	✓	-
[39]	Attenuated	✓	-	-	✓	-	✓	-	-	-	✓	-
[40]	Attenuated	✓	✓	✓	✓	-	✓	-	✓	✓	✓	✓
[41]	Inactivated	✓	✓	-	-	-	✓	✓	-	-	✓	-
[42]	Inactivated	✓	-	-	✓	-	✓	-	-	-	✓	✓
[43]	Inactivated	✓	-	-	✓	-	✓	-	-	-	✓	✓
[44]	Inactivated	✓	-	-	✓	✓	✓	-	✓	✓	✓	✓
[45]	Inactivated	✓	-	-	✓	-	✓	-	-	-	✓	-
[46]	Attenuated	✓	-	-	✓	-	✓	-	-	-	✓	-
[47]	Attenuated	-	✓	-	-	✓	✓	-	-	-	✓	-
[48]	Recombinant	✓	-	-	✓	-	✓	✓	-	-	-	-
[49]	Recombinant and inactivated	✓	-	-	✓	-	✓	-	-	-	✓	-
[50]	Attenuated and inactivated	✓	-	-	✓	-	-	-	-	✓	✓	-
[51]	Recombinant	✓	-	-	-	-	-	-	-	-	✓	-

Figure 2. Strategies for vaccine development, administration, and evaluation applied by referenced studies on Nile tilapia *Oreochromis niloticus*.

Table 3. Literature regarding experimental and commercial vaccines presented and discussed for Atlantic salmon *Salmo salar*. Approximate size refers to the fish BW at the time of challenge or RPS calculation, as stated in or inferred from references. In case of commercial vaccines, the product description was linked. Challenges must be intended as homologous except when stated otherwise. List of abbreviations: IFN—interferon; ISAV—infectious salmon anemia virus; IPNV—Infectious pancreatic necrosis virus; IHNV—infectious hematopoietic necrosis virus; SAV—salmonid alphavirus; PRV—piscine orthoreovirus; FCA—Freund's complete adjuvant; FIA—Freund's incomplete adjuvant.

Pathogen	Vaccine Status	Adjuvant	Approx. Size (g)	Challenge	Ref.

Tenacibaculum finnmarkense	Experimental	Mineral oil	26	Yes (homologous and heterologous)	[52]
Yersinia ruckeri	Experimental	No	9	Yes	[53]
Flavobacterium psychrophilum	Experimental	Squalene/alum or Montanide™ ISA 760 VG	23	Yes	[54]
Polyvalent	Commercial (Aquavac® PD7)	Paraffin	40	No	[55]
ISAV	Experimental	No	40	Yes	[56]
ISAV and *Piscirickettsia salmonis*	Commercial (Virbac-Centrovet)	Oil	40	No	[57]
ISAV	Experimental	IFNa- or IFNc	40	No	[58]
IPNV	Experimental	No	0.5 and 20	Yes	[59]
IHNV	NA	No	5 g	Yes (heterologous)	[60]
SAV	NA	No	Post-smolt	Yes (heterologous)	[61]
PRV	Experimental and commercial (ALPHA JECT micro® 6)	Paraffin	55	Yes	[62]
PRV	Experimental	No	35	Yes	[63]
SAV	Experimental and commercial (Norvax® Compact PD)	Montanide ISA 763A VG (only in the latter)	30	Yes	[64]
Cryptobia salmositica	Experimental	No	300	No	[65]
Caligus rogercressey	Experimental	Montanide™ 888 VG	80	Yes	[66]
Neoparamoeba perurans	Experimental	FCA (first immunization) and FIA (booster)	100	Yes (two, 5-week apart)	[67]
Lepeophtheirus salmonis	Experimental	Montanide™ ISA50 V2	90	Yes	[68]

		Delivery			Challenge		Evaluation strategy						
Ref.	Production strategy	Injection	Bath	Oral	Injection	Bath	RPS	Cell biology / Biochemistry	Histology	Pathogen count	Serology	RT-qPCR	NGS
[52]	Inactivated	✓	-	-	-	✓	✓	-	✓	-	✓	-	-
[53]	Inactivated	✓	✓	-	-	✓	✓	-	-	-	✓	✓	-
[54]	Inactivated	✓	-	-	✓	-	✓	-	✓	-	✓	✓	-
[55]	Inactivated	✓	-	-	-	-	-	-	-	-	✓	-	✓
[56]	Recombinant	-	-	✓	✓	-	✓	-	-	-	✓	✓	-
[57]	Not specified	✓	-	✓	-	-	✓	-	-	-	✓	-	-
[58]	Recombinant	✓	-	-	-	-	-	✓	-	-	✓	-	-
[59]	Recombinant	✓	-	✓	✓	-	✓	✓	✓	-	✓	✓	-
[60]	PVR infection	-	-	-	-	✓	✓	-	✓	-	✓	✓	-
[61]	PVR infection	-	-	-	✓	✓	✓	-	✓	-	-	✓	✓
[62]	Both inactivated	✓	-	-	✓	✓	-	✓	✓	-	-	✓	-
[63]	Recombinant	✓	-	-	-	✓	-	-	✓	-	-	✓	-
[64]	Recombinant and inactivated	✓	-	-	✓	-	-	-	✓	-	✓	✓	-
[65]	Attenuated	✓	-	-	-	-	-	✓	-	✓	✓	-	-
[66]	Recombinant	✓	-	-	-	✓	✓	-	-	✓	-	-	-
[67]	Recombinant	✓	-	-	-	✓	✓	-	✓	-	✓	✓	-
[68]	Recombinant	✓	✓	-	-	-	-	-	-	✓	-	✓	-

Figure 3. Strategies for vaccine development, administration, and evaluation applied by referenced studies on Atlantic salmon *Salmo salar*. For readability purposes, the bath and NGS columns also include cohabitation challenges and microarray experiments, respectively.

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