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Review

AUTOGENOUS VACCINES IN AQUACULTURE: TOOL TO COMBAT RESISTANCE OF BACTERIA TO ANTIBIOTICS?

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Abstract

New technological progress and increased demands for fish as a source of animal protein are driving significant growth of aquaculture production. Intensification of production increases the severity and frequency of infectious disease outbreaks, and so requires significant effort to prevent and control disease. Because of the global crisis of bacterial resistance to antibiotics, the use of antibiotics in aquaculture is increasingly subjected to strict control and regulatory measures, leading to potential misuse. The lack of availability of approved veterinary medical products for use in aquaculture, combined with the risk of drug resistance development and antibiotic residues in fish flesh or water, support the development of preventive actions, including vaccines. However, the diversity of species and aquaculture production methods, including epidemiological units and their links, results in economic challenges for commercial vaccine development and authorization. As a possible response to the increasing demand for less antibiotic use in fish farms, and to the expenses associated with novel veterinary product development, there is a need for increased use of safe and effective autogenous vaccines in aquaculture. Regulatory processes for autogenous vaccine production, approval and application should recognize the specificities of epidemiological units and their links in aquatic animal production facilities. The joint efforts of regulatory authorities, producers, and veterinary services to follow veterinary biosecurity principles, including risk analysis, surveillance, and selection/prioritization of pathogens, are

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essential to provide maximum safety and efficacy of autogenous vaccines as disease prevention and control tools within larger areas, such as compartments and zones, and allow for reductions in antibiotic use.

Key Words: autogenous vaccine, antibiotic resistant bacteria, antibiotic resistance, aquaculture, veterinary service

INTRODUCTION

Aquatic animal production has grown multiple fold in recent years, reaching over 90 million tons of product in 2021 (Fig. 1). The diversity of aquaculture is the highest of any of the animal production industries, and ranges from producing food fish to breeding ornamental/pet animals. Aquaculture currently encompasses over 500 cultured species, with more being added every year (FAO, 2022). Globally, the aquaculture regional leader is Asia (approximately 90% world production, with over 60% currently based in China). The aquaculture industry in the European Union (EU) is oriented on fewer species with the focus on marine fish aquaculture (Atlantic salmon, sea bass, and sea bream), and accounts for ~2% of global aquaculture production (FEAP, 2021). European aquaculture is a highly regulated sector in the area of environmental protection. EU regulations also apply regarding health and biosecurity, with access to medicines, including vaccines and autogenous vaccines specifically intended or approved for use in designated species, being severely limited (Doherty et al., 2019). The specifics of aquaculture production systems are variable and complex. The majority of aquatic animals are produced in open surface waters using cages,

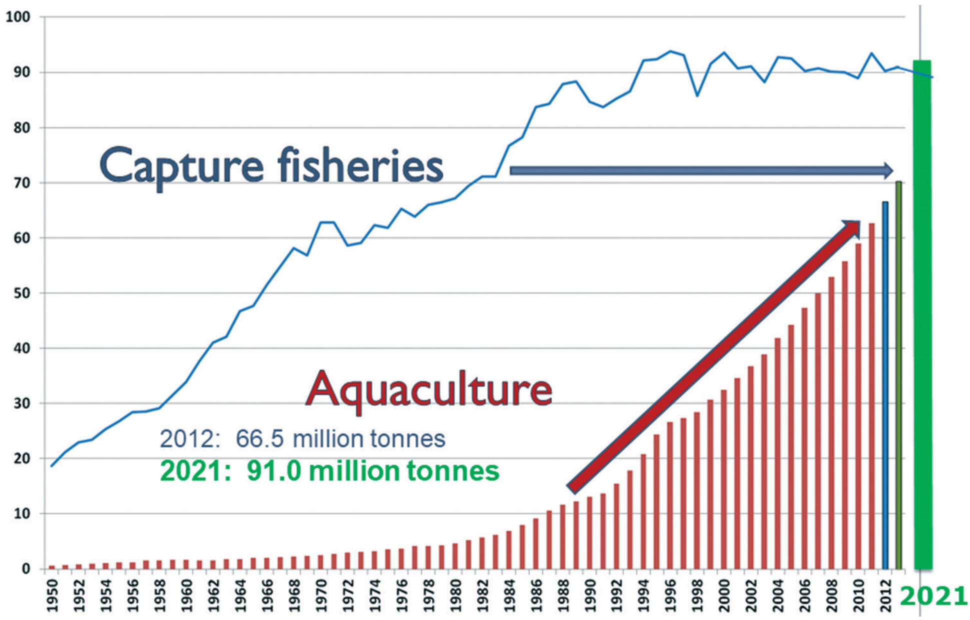

Figure 1. Annual global production of aquaculture and capture fisheries 1950-2021 (in million tons). Prepared and modified from FishstatJ (FAO 2018)

ponds, or raceways, but with the involvement of indoor production in parts of the life cycles (mostly hatcheries). Ownership structures of aquaculture businesses range from individual small-scale producers to large multinational corporations with elaborate production chains and "in-house" vertical integration, from selection and broodstock to final products ready for retail sales. With such diversity of production systems and business interests, combined with regulatory limitations regarding veterinary medical products, it is exceedingly difficult to address the prevention and control of infectious diseases in aquacultured food fish (Palić and Scarfe, 2018).

In an attempt to standardize aquatic animal disease prevention and control terminology, the WOAH (World Organisation for Animal Health) Aquatic Animal Health Code and Manual (WOAH, 2021) introduced numerous definitions that will be used to describe specific conditions of various epidemiological aspects in aquaculture establishments, along with those pertaining to autogenous vaccines. The most important definitions for our purposes are:

An *Aquaculture Establishment* is an establishment (e.g. farm) in which amphibians, fish, mollusks or crustaceans for breeding, stocking, or sale are raised or kept. An *Epidemiological Unit* is a group of animals that share approximately the same risk of exposure to a pathogenic agent within a defined location (Scarfe and Palić, 2020). This can be because they share a common aquatic environment (e.g. fish in a pond, caged fish in a lake), or because management practices make it likely that a pathogenic agent in one group of animals would quickly spread to other animals (e.g. all the ponds on a farm, all the ponds in a village system). A *Compartment* is one or more aquaculture establishments (farms) under a common biosecurity management system containing an aquatic animal population with a distinct health status with respect to a specific disease or diseases for which required surveillance and control measures are applied and basic biosecurity conditions are met for the purpose of international trade. Such compartments must be clearly documented by the Competent Authority. A *Zone* is a portion of one or more countries comprising: an entire water catchment from the source of a waterway to the estuary or lake, or; more than one water catchment, or; part of a water catchment from the source of a waterway to a barrier that prevents the introduction of a specific disease or diseases, or; part of coastal area with a precise geographical delimitation, or; an estuary with a precise geographical delimitation, that consists of a contiguous hydrological system with a distinct health status with respect to a specific disease or diseases. The zones must be clearly documented (e.g. by a map or other precise locators such as GPS co-ordinates) by the Competent Authority.

An EpiUnit can be small (an individual farm or "establishment", or parts of a farm), or large (several farms, a state or province, watershed, or a whole country). Any geographic area that somehow separates one group of animals from another can be an EpiUnit, *providing* that all animals in one unit are managed in a similar way. The separation can be a physical barrier, or simple separation by distance – but the animal population in each EpiUnit *must not co-mingle* with animals outside the EpiUnit.

More broadly, the EU regulations mention "epidemiological unit" as a group of animals with "the same likelihood of exposure to a disease agent" (EU-Regulation 2016/429, Article 4 No. 39; EU, 2021) and "animals in units having a confirmed epidemiological link" (EU-Regulation 2019/6, Article 2 (3); EU, 2022). The specifics of aquatic animal production were recently recognized (Grein et al., 2022). Here, the two most relevant characteristics of aquaculture production sites are mentioned as: 1) "for the special situation of the aquaculture, it should be highlighted that pathogens can move freely into the environment. Animals can therefore be in contact with pathogens without being moved between sites"; and 2) " …for aquatic animals, an epidemiological link also exists between different farms/sites within one geographic area; where an identical pathogen is circulating and spread e.g. by wild aquatic species."

The WOAH clearly expands the concepts of EpiUnits to larger geographic units, allowing for different interpretations of the existing regulations. From this perspective, although this section is focused on application and use of autogenous vaccines in aquaculture establishments, it is very important to emphasize that aquatic animals sharing the same watershed connection are at higher risk of being exposed to the same pathological agent, when compared to terrestrial animal production in the same geographical area. Therefore, regulations for autogenous vaccine production, approval, and application should recognize these specifics in order to provide the maximum safety and efficacy of autogenous vaccines as disease prevention and control tools within larger areas such as compartments and zones (Scarfe and Palić, 2020).

Use of autogenous vaccines in aquatic animal production. Development of fish vaccines and vaccination strategies has rapidly changed the aqua-scape of antibiotic use in a fast growing industry. Norway's example of a success story from the 1990s demonstrated that the use of antibiotic treatments in the salmon industry can be reduced to a minimum with vaccination programs and improvements in biosecurity practices (NVI, 2016). However, the current situation regarding veterinary medical products, including biologicals and biocides specifically approved for use in aquaculture of food fish is severely limiting access to legal options that can be used by veterinarians for the treatment and control of infectious aquatic animal diseases (Doherty et al., 2019). The recent EU regulation 2019/6 and new animal health laws derived from this directive have since been supplemented with various addendums to address some of the problems that have been identified, including more uniform standards for autogenous vaccine production and use in food fish aquaculture (EU, 2022).

So far, autogenous vaccines in finfish aquaculture have been used with variable success (Adams, 2019). Inherent issues, such as pathogen diversity, different field conditions, and multiple vaccine application techniques, have contributed to this variability. Furthermore, standardization of production process quality control and assurance has been generally missing across EU member states. The European manufacturers of autogenous vaccines (EMAV) is spearheading efforts to set industry standards for autogenous vaccine production, and it is expected that regulatory agencies will recognize the benefits of safe and efficient aquaculture autogenous vaccines, which are a much desired addition to the aquatic veterinarian's toolbox (EMAV, 2021).

The diversity of aquaculture production systems, species, and enterprise sizes are effectively preventing descriptions of and discussions on every specific situation, especially within the limitations of the first edition of the EMAV proposal. Therefore, it is currently only possible to focus on common approaches using the EpiUnit approach and discussing the basic principles of aquatic animal infectious disease control and prevention by the application of autogenous vaccines as a part of a comprehensive EpiUnit biosecurity program (Scarfe and Palić, 2020). It is expected, however, that specific case studies will be made available as examples of autogenous vaccines' utility in the future (Scarfe and Palić, 2017). It is suggested the following steps are taken into account when discussing the possible use of autogenous vaccines in aquatic animal disease control and prevention:

Assessment of existing and potential hazards and risks associated with the specific EpiUnit. In order to determine what diseases might be hazards that could severely affect the EpiUnit, it is suggested a semi-quantitative (weighted) approach is used to estimate the risks and impacts of each disease and prioritize the diseases for inclusion in the vaccination program. For more simple EpiUnits, where the use of cumulative scores (sum of risk and impact scores) is suitable, the first step would be to select the highest-ranking diseases to include as candidates for autogenous vaccine development for the specific EpiUnit (Fig. 2). Nonetheless, in more complex EpiUnits such as larger farms, compartments, zones, or countries/regions, a more formal risk assessment process is likely needed in order to provide better estimates of priorities and associated actions to be developed for the disease control and prevention program (e.g. use of the FAO Risk Assessment tool) (Bondad-Reantaso et al., 2009).

		Consequences				
		Insignificant	Minor	Moderate	Major	Severe
Likelihood	Almost Certain	Medium	High	High	Extreme	Extreme
	Likely	Medium	Medium	High	Extreme	Extreme
	Possible	Low	Medium	Medium	High	Extreme
	Unlikely	Low	Low	Medium	High	High
	Rare	Low	Low	Low	Medium	High

Figure 2. A generic, qualitative risk-consequences chart useful for estimating the impact of a disease on an EpiUnit. To prioritize diseases considered to be hazards to the EpiUnit, the semi-quantitative impact (I) can be calculated by assigning a value (1-10) to each consequence (C) and likelihood (L) and used in a formula [I = C x L] to establish disease rankings. The highest-ranked diseases should then receive the most attention when developing the biosecurity plan for the EpiUnit, particularly when resources are limited. Adapted from Scarfe and Palić (2020).

The expected output from this step is a prioritized list of diseases (in a suitable format, e.g. Fig. 3) with past, current, or potential serious impacts on the EpiUnit, i.e. those hazards that severely decrease production, are zoonotic, would cause unacceptably high morbidity or mortality, would result in regulatory restrictions, would negatively affect the reputation or economic viability of the unit, or might have serious impacts on wild populations or other units in the region. The list should not only include those diseases that are reportable to a governmental agency, but should also include diseases the owner feels are important.

Identifying & Prioritizing Disease Hazards Using a Simplified, Semi-quantative Risk-Impact Analysis

Instructions: Based on the general knowledge of the group, quantify 3-4 viral, bacterial, parasitic, or other diseases that might impact this farm.

Score: ***1. Presence*** (Not in EU = 1, In country=5, On farm=10); ***2. Affect farm*** (0=no likelihood, 10=very likely); ***3. Impact*** (None=0, 10=very high)

Viral Diseases					
1. Disease present?	**2. Likelihood will affect farm?**	**3. Impact on farm?**	**Describe Impacts on Farm (e.g. production, morbidity, mortality, zoonotic, regulatory depopulation, etc.)**	**Total Score (1x2x3)**	**Rank 1=highest**
Bacterial Diseases					
Parasitic Diseases					
Other Diseases					

Figure 3. Example of semi-quantitative risk-impact analysis spreadsheet to be used for identification and prioritization of disease hazards in an aquaculture establishment. Adapted from Scarfe and Palić (2017).

Selection of pathogen candidates for autogenous vaccine development in the EpiUnit. The conventional approach for autogenous vaccine production, also most frequently enforced by the regulatory authorities, is to sample and isolate a pathogen from the affected EpiUnit population, then cultivate it in the required quantities and inactivate it using approved methodology (Saléry, 2017). Using the prioritized disease list for the EpiUnit (farm, establishment, compartment, zone), it is necessary to select candidate(s) with the highest cost-benefit potential for the operation that will, at the same time, comply with the regulatory requirements of the respective country. In practical terms, most frequently, the pathogen(s) suitable for autogenous vaccine production and application belong to the domain of the bacteria, and in rare cases, parasites (e.g. *Philasterides dicentrarchi*). Viruses are not routinely considered as candidates for fish autogenous vaccines; however, several manufacturers have produced and applied viral autogenous vaccines in aquaculture (Barnes et al., 2021, Thwaite et al., 2022).

Species of bacterial pathogens presenting as high concern for aquaculture operations differ to some extent between freshwater and marine ecosystems, as well as between warm- and cold-water fish species. Most frequently however, they belong to Gram-negatives such as *Aeromonas* spp., *Vibrio* spp., *Flavobacterium* spp., *Yersinia* spp., *Pseudomonas* spp., and *Pasteurella* spp.. Less common are the Gram-positives, *Streptococcus* spp., *Renibacterium* spp., *Clostridium* spp., or acid-fast bacteria belonging to *Mycobacterium* spp., *Nocardia* spp., etc. (Pridgeon and Klesius, 2012). It is important to note that many (bacterial) pathogens (and their respective strains/isolates) can be present in fish without clinical symptoms, as well as in surface water sources and wild aquatic animal populations (as hosts or carriers, also including invertebrates, birds etc.). From the autogenous vaccine development and use perspective, this situation can require that epidemiological links between current and potential disease outbreak sites are subjected to thorough analysis, possibly with the assistance of geographical information system-based models (Feng et al., 2022).

As most of the aquacultured species (except Atlantic salmon – *Salmo salar*) currently belong to the category of minor use minor species (MUMS), the prophylactic approaches are frequently not a high priority for big companies, considering the costs associated with registration of commercial vaccines (Jungbluth, 2022). On the other hand, while the cost of autogenous vaccines is less prohibitive, the regulatory environment can be overly restrictive in interpretation of "one farm-one pathogen" language in the national legislation. It is becoming more obvious that EpiUnits in aquaculture could require broader implementation of prophylaxis, based on common antigenic determinations of a strain that is widespread in the corresponding establishment (farm), compartment, or zone (watershed) (WOAH, 2021). The analogy would be us putting out only parts of a forest fire, but leaving hot spots in the neighborhood unattended, only because administratively they belong to a different establishment, in which case, the fire is likely to come back and spread further. Similarly, if the isolate or strain of the pathogen is common within a watershed with multiple establishments, vaccinating only one (sub)population is a less than optimal use of resources, and with doubtful results regarding disease control within the area.

Autogenous vaccine use in disease control and prevention from the aspect of reducing antibiotic usage. Bacterial resistance to antibiotics is a global public health problem with special attention focused on the food supply as a part of the One Health program that combines veterinary medicine, the environment, and public health (Barnes et al., 2021). Intensification and diversification in aquaculture increases the frequency and intensity of infectious disease outbreaks, and can produce high mortality rates (Algammal et al., 2020). Prevention and control of diseases are challenging in aquaculture, and the first response to a disease outbreak is usually to initiate treatment of the affected population with chemical agents, including antibiotics, often without veterinary involvement and proper diagnosis (Smith et al., 2008). Such approaches lead to excessive and/or incorrect use of antibiotics in aquaculture, contributing to the problem of antibiotic resistant bacteria (Cabello et al., 2016).

In addition to the amount and frequency of antimicrobial use in aquaculture around the world, the type of antibiotics used is increasingly problematic, even if regulatory restrictions are posed to allow use of only a few antibiotics in food fish. For example, the only antibiotics approved for use in aquaculture in the United States are oxytetracycline, florfenicol, and sulfadimethoxine/ormetoprim (Love et al., 2020). In stark contrast, recent surveys found a total of 23 antibiotics from 11 different classes used by Vietnamese fish and shrimp farmers (Luu et al., 2021). In Malaysia, antibiotic residue testing in pond water also revealed traces of 23 antibiotics from 6 different classes (Thiang et al., 2021). These reports suggest limited efficacy in preventing a misuse of antibiotics, especially in imports from areas with limited aquatic veterinary workforce availability (Henriksson et al., 2018). It is often the case that antibiotic therapy is carried out without isolation of the causative agent and antibiotic susceptibility testing, applying wrong doses and application routes, and not respecting the withdrawal period (Luu et al., 2021). Such uncontrolled use of antibiotics contributes significantly to the development and maintenance of antibiotic resistance in bacteria isolated from farmed fish, crustaceans and shellfish, simultaneously reducing production results and having a negative impact on the environment.

Currently, a significant contrast exists between the ease of access and availability of antibiotics (regulated or illegal) and the difficulty in vaccine (including autogenous vaccines) approval regulatory processes. Current regulations do not take into account the advances in technology that allow for the advantages of locally produced autogenous vaccines to be used in aquatic animal disease prevention and control. Isolation and identification of bacteria isolates from aquaculture establishments is becoming easier, faster, and cheaper with the recent developments in sequencing technology and bioinformatics. Improvements in methods for cultivation and inactivation of locally isolated bacteria are now common knowledge and can be practiced by clinical veterinary microbiology specialists. These factors allow (autogenous) vaccine manufacturing processes to easily adjust and quickly deliver final products that reflect the changes in the disease-causing isolates within the affected establishments (Barnes et al., 2021). Norwegian aquaculture is a good example of the successful transition from treatment to prevention of fish diseases through the introduction of vaccination against major bacterial diseases, enabled by a supportive regulatory regime that promoted vaccine use and severely limited access to antibiotics through more restrictive maximum residue levels (Barnes et al., 2021; Sommerset et al., 2005).

CONCLUSION

In light of the global crisis of bacterial resistance to antibiotics, further encouragement is needed to accelerate safe and reliable production and application of autogenous vaccines in aquaculture. This fast and relatively simple technology has great potential to be applied within the restrictions of EpiUnits, to reduce the use of antibiotics, and to minimize the occurrence of antimicrobial resistant bacteria in aquaculture.

Therefore, the utility of autogenous vaccines in aquaculture strongly depends on the relationship between producer, veterinarian, and government. It is strongly correlated with the use of veterinary biosecurity principles, including risk analysis, surveillance, and selection of pathogens suitable for autogenous vaccine application in an EpiUnit of concern. As part of the overall biosecurity strategy, and with the use of current technologies to select the best candidates and produce standardized vaccine at reasonable cost, autogenous vaccines have the potential to become a powerful tool in aquatic animal disease control and prevention, and to play a significant role in reducing antibiotic use in aquatic animals.

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Authors' contributions

DP prepared initial draft of the text and figures. KA reviewed and contributed to sections and improvement of the text. DP and KA finalized the manuscript for submission.

Competing interests

The authors declare that they have no competing interests.

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AUTOGENE VAKCINE U AKVAKULTURI: SREDSTVO ZA SMANJENJE OTPORNOSTI BAKTERIJA NA ANTIBIOTIKE?

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Kratak sadržaj

Nove tehnologije u proizvodnji i povećana potražnja za ribom kao izvorom životinjskih proteina glavni su razlozi rasta proizvodnje u akvakulturi. Intenziviranje produkcije povećava frekvenciju i intenzitet izbijanja infektivnih bolesti, i zahteva značajan napor prilikom prevencije i kontrole bolesti. Zbog globalne krize u vezi sa antimikrobnom rezistencijom, upotreba antibiotika u akvakulturi je sve više pod strogom kontrolom i regulatornim merama, što dovodi i do njihove upotrebe bez veterinarskog nadzora. Nedostatak odobrenih veterinarskih lekova u akvakulturi u kombinaciji sa povećanim rizikom od razvoja rezistencije na lekove i problema u vezi sa reziduama antibiotika u mesu riba ili vodi, upućuje nas na korišćenje preventivnih mera, uključujući tu i vakcine. Medjutim, raznolikost vrsta i medoda gajenja u akvakulturi, kao i povezanosti epidemioloških celina, dovodi do ekonomskih teškoća i izazova u proizvodnji i odobrenju komercijalnih vakcina za upotrebu u zdravstvenoj zaštiti riba. Jedan od mogućih odgovora na zahteve za smanjenom upotrebom antibiotika na farmama riba, kao i troškova vezanim za razvoj i odobrenje novih veterinarskih lekova, bi bila povećana upotreba sigurnih i efektivnih autogenih vakcina u akvakulturi.Propisi za proizvodnju, odobrenje i primenu autogenih vakcina treba da budu u skladu sa specifičnostima povezanosti epidemioloških celina u proizvodnji riba. Zajednički napori veterinarske struke, vladinih agencija i proizvodjača da slede principe biosigurnosti, analize rizika, zdravstvenog nadzora i prioritizacije patogena su neophodni u cilju obezbedjivanja maksimalne sigurnosti i efikasnosti autogenih vakcina u okviru većih celina (kompartmana ili zona), što bi dovelo i do smanjenja upotrebe antibiotskih tretmana.

Ključne reči: autogene vakcine, antimikrobna rezistencija, akvakultura, veterinarske usluge