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REVIEWS IN Aquaculture

REVIEW

Autogenous vaccination in aquaculture: A locally enabled solution towards reduction of the global antimicrobial resistance problem

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Abstract

Antimicrobial resistance is a global public health crisis with attention focussed on food supply as part of the 'One Health' integration of veterinary, environmental and public health. Aquaculture has been the fastest growing livestock sector in recent decades and is critical to nutritional security in many low- and middle-income countries (LMIC). With ready access to antibiotics and limited availability of veterinary support, disease control with antibiotics is poorly informed, often unrecorded and high in many countries where aquaculture growth is fastest. Vaccination of fish in LMIC with locally produced autogenous vaccines against bacterial diseases may provide a locally driven, cost-effective means of reducing antibiotic use, replicating the successes achieved during the growth of Norway's aquaculture industry. Autogenous vaccines, as part of an informed veterinary health programme, have several advantages in terms of intellectual property, efficacy and flexibility. We consider access to fish vaccines in example countries of high aquaculture importance, including Thailand, Vietnam and Indonesia. We contrast the success of antimicrobial reduction in Norwegian salmon aquaculture with the high antibiotic use in the Chilean industry where vaccines are available, finding that regulation, planning, husbandry and environmental problems may increase disease incidence and severity. We identify technical, bureaucratic and infrastructural transitions that could facilitate implementation of autogenous vaccination in LMIC aquaculture against challenging socio-economic and environmental backgrounds. The benefits of autogenous vaccination to animal welfare, transboundary biosecurity, local farmer and industry economics, and to public health, favour implementation in aquaculture as a locally enabled solution to the global problem of antimicrobial resistance.

KEYWORDS

antibiotic, antimicrobial resistance, aquaculture, one health, vaccines

1 | BACKGROUND

Aquaculture, the farming of fish and shellfish, currently underpins nutritional security in low- and middle-income countries (LMIC) throughout Asia. It is also growing rapidly in sub-Saharan Africa and South America. The farming of freshwater fish, such as carp, tilapia and catfish, provide the majority of locally consumed fish,[1] supplying key nutrients that are critical to healthy childhood development. Thus, disruptions in aquaculture production in those countries can have pronounced consequences for human health. Diseases caused by bacteria and viruses in aquaculture account for direct losses estimated at $6 billion in production in 2014.[2,3] Additionally, the use and misuse of antimicrobials to attempt to control disease outbreaks in farmed fish[4,5] select for antimicrobial resistance (AMR),[6] exacerbating the AMR crisis in veterinary[7] and public health.[8] Since the early 2000s, there has been a growing movement to integrate the traditionally separate disciplinary approach to human, animal and environmental health research and policy into a more holistic 'One Health' approach, recognising the interconnected reality of people, animals and planet.[9] AMR represents a global 'One Health' challenge requiring a multi-domain consideration of the drivers of AMR including food production.[10] Not surprisingly, given the growth and importance of aquaculture in global food security, consideration of the AMR risk during aquatic food production is gaining attention from a 'One Health' perspective.[11]

Antibiotics are used worldwide during aquaculture production in response to disease, particularly in intensive rearing systems.[12] Accurate quantitative data on antibiotic use in LMIC, as in many advanced economies, are difficult to obtain.[4] Chile is an exception with annual government reports on antibiotic use. In 2020, 379,600 kg of antibiotics were used in Chilean salmon production.[13] Elsewhere, qualitative information based on questionnaires and measured presence of antibiotics in surface waters suggests use in intensive finfish rearing systems such as tilapia and pangasius catfish is significant.[14-16] For example, in Vietnam in 2007 more than 80 mg antimicrobial agents (sulfamethoxazole, cephalexin, amoxicillin, florfenicol and enrofloxacin) were estimated to be used for each kg of pangasius catfish produced.[16] If, for example, 30 mg of antibiotics is used per kg of production of tilapia (6.37 million tonnes production in 2014) and pangasius (2.7 million tonnes), it would equate to more than 272,000 kg of antibiotic alone in the two main intensively reared finfish species in LMIC. More recently, a survey in 2020 revealed 23 antibiotics comprising 11 different classes in use by Vietnamese fish and shrimp farmers, with 64% of fish farms and 24% of shrimp farms surveyed self-reporting use of antibiotics.[17] In Malaysia, antibiotic residue testing of farm water detected 23 antibiotics belonging to six classes present, albeit at very low concentration at all but one site.[18] Antibiotic treatments may be conducted without determination of the pathogen identity, antibiotic susceptibility and treatment dose requirements and compliance with withdrawal periods.[5,17] There is naturally concern that such unguided antibiotic use drives the development and maintenance of resistance in pathogens of farmed fish and shellfish, reducing productivity and adversely impacting animal welfare. Moreover, environmental discharge of antibiotics via aquaculture likely has a role in the wider development and dissemination of AMR and its acquisition by human pathogens[19] and additional deleterious effects on the health of the receiving ecosystem.[18] Rapid recourse to inexpensive, easily accessible antibiotics where economic exclusion may hinder access to skilled veterinary advice may mean that the contribution of husbandry, water quality, feeding regime, farm design and nutrition to disease expression is overlooked. Thus, the opportunities for disease control and concomitant reduction in antimicrobial use through correction of these risk factors are missed.

Norway faced a similar challenge of antimicrobial overuse in the mid-late 1980s during the growth of the salmon farming industry, with highest recorded antibiotic use of 48,570 kg to produce 80,000 tonnes of salmon in 1987, equivalent to 607,125 mg/tonne.[20] In contrast, just 1037 kg antibiotic was used to produce 290,000 tonnes in 1996 (358 mg/tonne).[21] Moreover, there was a decrease in the numbers of antibiotic treatments from 1697 in 1991 to only 99 in 2000. Meanwhile, production increased from 160,700 tonnes to 482,503 tonnes over the same period.[22] In 2019, the Norwegian salmon industry used 222 kg of antimicrobials to produce 1,375,307 tonnes (160 mg antimicrobial per tonne).[23] This transformation from treatment to prevention of disease in farmed fish was achieved through the introduction of vaccination against the major bacterial diseases,[24] accompanied by a supportive regulatory regime which promoted vaccine use and tightened access to antibiotics through more restrictive maximum residue levels (MRL). The vaccines were technologically simple formalin-inactivated bacterial cultures, formulated as water-in-oil emulsions using a mineral or vegetable oil and delivered by a single injectable dose into the peritoneum of the animal under anaesthetic, which protected the animal for its life.[25] These vaccines were developed and produced locally by relatively small private companies (eg Norbio, Apothekernes Laboratorium) and, as the industry grew, internationally (eg Intervet from Netherlands, and Aqua Health from Canada).[26] The Norwegian salmon industry consolidated through the 2000s, and in 2019, it produced 812,410 tonnes of salmon amongst relatively few large companies.[27] During the late 1990s and early 2000s, the smaller biologicals companies that pioneered vaccination of fish in Norway were acquired by global pharmaceutical and agrichemical businesses such as Merck Sharp & Dohme (Norbio, Intervet, AVL), Elanco (Aqua Health *via* Novartis Animal Health) and Zoetis (Apothekernes Laboratorium/Alpharma/Pharmaq).

Replicating the Norwegian success in tropical and sub-tropical aquaculture should be a priority but faces a number of technical, social, environmental and economic challenges that were not present in Norway in the 1980s. These include lack of accessible diagnostics, limited farmer support and education, lack of clear regulatory framework with functional compliance mechanisms to limit antimicrobial use, and the diversity of major bacterial diseases, in addition to the time and financial costs of developing registered vaccines[4,5,28](Figure 1). Fish farming in developing countries throughout Southeast Asia and Africa comprises 100s to 1000s of smallholder

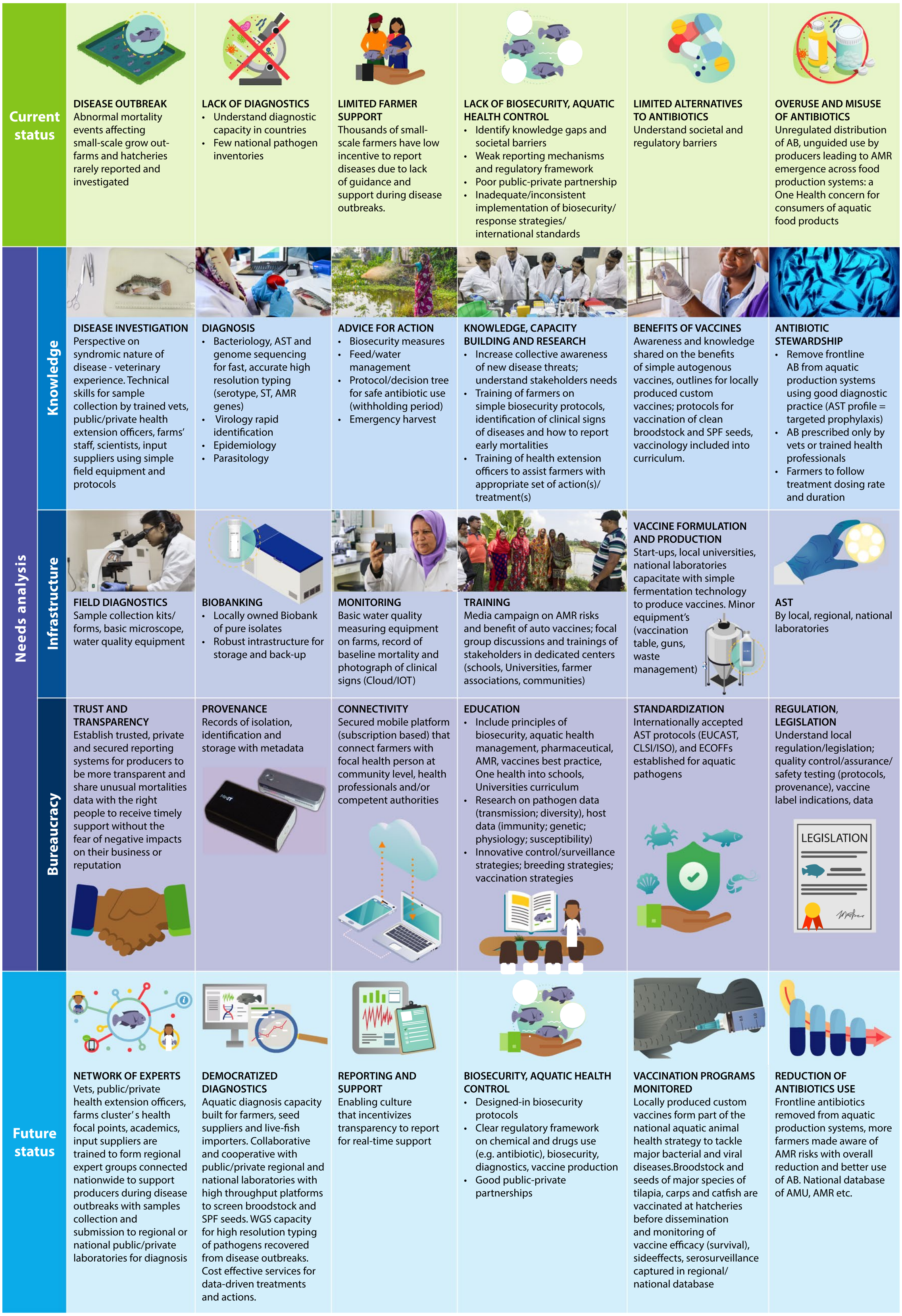

FIGURE 1 Tentative needs analysis for increasing uptake of autogenous vaccination as part of a cost-effective, locally implemented aquatic animal health platform to reduce antibiotic use in finfish aquaculture in developing economies. Abbreviations: AB, antibiotics; AMR, antimicrobial resistance; AST, antimicrobial susceptibility testing; CLSI, Clinical and Laboratory Standards Institute; ECOFFs, Epidemiologic cut-off values; EUCAST, European Committee on Antibiotic Susceptibility Testing; ISO, International Organization for Standardization; IOT, internet of things; SPF, specific pathogen free; ST, sequence type; WGS, whole genome sequence

and small-medium enterprise farmers on a per-country basis, but is undergoing some consolidation and intensification in favour of the latter.[29] Nevertheless, there are factors in addition to market fragmentation that makes freshwater fish farming in the global south unattractive for corporate investment in the development of licensed vaccines. For example, the lower value of the fish produced, both in terms of price per kg (~$1) and also the size of fish sold into the market (<1 kg for tilapia and carp), reduces the per-dose price that farmers may be able and willing to pay for vaccinated seed stock. Secondly, the diversity and rapid evolution of diseases amongst freshwater fish, particularly in warm water, are incongruous with the development and licensing timescales of fully registered vaccine products.[28,30] For these challenging farming environments, there are both economic and biological drivers that demand a faster and more flexible approach.

1.1 | Autogenous vaccines are effective and flexible

Autogenous (auto) vaccines are custom vaccines produced from pathogens isolated directly from affected farm(s) on which the vaccines are subsequently deployed under a minor use or restricted permit. In terrestrial agriculture, auto-vaccines have been very effective in cattle, swine and poultry[31-34] and successfully reduced antibiotic use.[31] For example, deployment of an autogenous vaccine against *Staphylococcus hyicus* in pigs reduced antibiotic use for control of exudative epidermitis by more than 60%.[31] Auto-vaccines are also used in aquaculture and have been effective against atypical *Aeromonas*,[35] novel biotypes of *Yersinia ruckeri* [36,37] infections in salmonids, Streptococcal pathogens in barramundi and stingrays[30,38,39] and, in Tilapia, autogenous vaccines against the intracellular pathogen *Francisella noatuensis* have been shown to be effective.[40] In Australia, a mix of licensed and autogenous vaccines are used in finfish aquaculture reflecting the diversity of scales of the sectors. For example, a licensed vaccine against *Y. ruckeri* is employed in the consolidated Atlantic salmon industry (worth $892 million 2019), whereas autogenous vaccines against *Streptococcus iniae* are successfully used in the smaller and much more fragmented barramundi (Asian sea bass) farming industry (worth $53.6 million in 2018). Interestingly, in spite of the large size of the Australian Atlantic salmon industry, autogenous vaccines, including custom multivalent vaccines, are also employed under minor use permits, rather than through full registration.

Apart from the shorter development track for autogenous vaccines, they are more efficient against the local serotypes of variable pathogens and faster to produce/re-formulate compared to licenced commercial vaccines. Moreover, production of commercial generic vaccines that are efficient in the long-term without necessity of re-formulation may not be achievable against pathogens with rapidly evolving highly variable antigens.[41-44] While emergence of vaccine resistance is less alarming than antibiotic resistance, novel serotypes continue to arise despite, or even in response to, implementation of multi-serotype vaccines in humans.[45] Notably, pathogen evolution in the freshwater environment is evidently faster than in terrestrial as well as marine habitats.[46] Consequently, disease outbreaks in immunised populations (vaccine escapes) caused by novel serotypes are inevitable and inclusion into a licensed commercial formulation may take years in the absence of an autogenous vaccine regulatory framework. Furthermore, attempting to produce cross-serotype licensed vaccines by mixing many antigens may reduce efficacy as antigenic competition reduces protection against the attacking strain.[47,48] Thus, autogenous vaccines that can be more specifically targeted for each crop overcome this problem. Additionally, the high specific efficacy of autogenous vaccines and their rapid implementation in response to threats is of primary epidemiological significance as it may prevent or slow the spread of locally emerging pathogen serotypes to the wider area.

Evidence-based formulation of auto-vaccines is critical to their advantages in terms of efficacy over fully licensed alternatives. This requires appropriate knowledge for correct field and laboratory diagnosis (Figure 1), with collection of an appropriate range of samples to have confidence that the identified microbe is actually the cause of the disease being expressed. It is very easy to culture and identify the wrong microbe in field sampling. Multiple modalities of laboratory diagnostics are required to complement and consolidate the field diagnosis including histopathology, microbiology and, at times, molecular biology. All diseases are the consequence of the interface of pathogen, host and the environment. Hence, a skilled aquatic field veterinary capacity is critical to identify the co-contributory risk factors and design appropriate mitigations. Upon accurate causative diagnosis indicating that vaccination may be a useful preventative strategy, autogenous vaccines require both the correct antigens, and mixed with an adjuvant appropriate to the species and farming condition. Recent advances in genomics have increased the speed and accuracy, as well as dramatically reducing the cost, of pathogen typing. This includes rapid identification of key antigenic variants in capsular and lipopolysaccharide O-antigens that underlie serotype-specific protection by formalin-killed vaccines for gram-positive and gram-negative bacteria, respectively.[37,39,49,50] In terms of adjuvant, the routine formulation of vaccines as water-in-oil emulsions was the major breakthrough technology in the 1990s that substantially increased the potency, but most importantly extended the duration of immunity afforded by a single dose to the entire farm lifecycle from nursery to harvest (at the time, around 4 years for salmon in water ranging from 8–17°C).[24,51-53] Adjuvants may require optimisation for the tropical and sub-tropical farm cycle and conditions (6–12 months, 20–34°C). However, there are off-the-shelf products available with documented safety profiles and there is opportunity to fine-tune antigen delivery and specific antibody response for the conditions via manipulation of emulsion droplet size and oil biodegradability.[54-56]

Killed autogenous vaccines are simple to produce in small batches without need for very expensive facilities and equipment, provided that controlled standard operating procedures are in place. This means that they can be produced within the country where they are deployed. Local production has a major advantage in terms of protection and retention of the indigenous biological resource, which becomes locally owned so that the benefits that flow from it accrue to local people.[57] Disease-causing strains and serotypes, along with their genetic description, constitute a valuable local resource. Too often, these are removed and exploited by global corporations or wealthy nations (termed biopiracy or neo-colonialism), a problem that the Nagoya Protocol attempts to address.[58] It is contended that local production, afforded by the relative simplicity of autogenous vaccines, fixes many of the limitations identified in the Nagoya Protocol, particularly around access and public-private partnership to protect and allow access to developed resources post-commercialisation.[58] Moreover, local manufacture of vaccines provides business and career development opportunities for biological and health science graduates within the country. With the right partnerships and policies in place, there is clear opportunity to contribute positively to the balance of skilled migration in low- and medium-income countries.[59] A further advantage of local production of vaccines is the elimination of the biosecurity risk and border control costs involved in import and export of biological products.

1.2 | Current status in example countries

Indonesia: The Indonesian government through the Ministry of Maritime Affairs and Fisheries from 2012 to 2015 encouraged aquaculture industrialisation, including the use of fish vaccines nationally in fish cultivation centres. This programme was known as the Fish Vaccination Movement (Gerakan Vaksinasi Ikan, GERVIKAN) and was implemented through demonstrations on how to use vaccines, along with provision of cheap vaccines and certified vaccinators. The aim of GERVIKAN was to disseminate vaccines that are safe, effective and inexpensive, as an effort to control fish diseases. Moreover, GERVIKAN encouraged the provision of vaccines by microbial isolate providers and fish drug manufacturers to mass produce vaccines from local isolates. However, the demand for fish vaccines of a particular type was insufficient at the time, to drive a local vaccine industry, largely through lack of farmer awareness. Consequently, most of the fish vaccines used in now Indonesia are imported (Table 1). While vaccine candidate isolates are collected and retained by many research institutions and universities in Indonesia, the technology transfer to industry needs to be facilitated and encouraged by the Government. Reactivation of GERVIKAN would be beneficial to aquaculture businesses in Indonesia as the extension and education capacity for farmers are now improved, especially the Integrated Fish Health Co-Service Extension (POSIKANDU), which has more than 50 POSIKANDU distributed throughout Indonesia.

Vietnam: Since 2006, significant research has evaluated various vaccine types funded by the Vietnamese Government. Experimental vaccines against *Edwardsiella ictaluri* conferred high protection and efficacy in Pangasius catfish using a heat-shock protein vaccine and a live attenuated vaccine. However, none of these products have been commercialised. In 2013, a bivalent vaccine against *Aeromonas hydrophila* and *E. ictaluri* infection in Pangasius catfish was developed by Stirling University and Norwegian fish vaccine company Pharmaq (a subsidiary of Zoetis). This was commercialised in Vietnam in 2016 as an injection vaccine ALPHA JECT Panga 1. Recently, a new vaccine for prevention of *Streptococcus iniae* and *S. agalactiae* infection in Tilapia was licensed for commercial use in Vietnam by local company HANVET (Table 1). However, a comprehensive and systematic approach to aquatic vaccination has not been applied to date in Vietnam, which has resulted in farmers not using available vaccines and instead of taking a fragmented approach to disease management. Although fish vaccination is the most cost-effective approach to disease control, it is a relatively new concept for many Vietnamese farmers. Consequently, implementation will only be effective if delivered to the farmers through training programmes.

Thailand: Thailand is one of the major producers of tilapia and Asian sea bass where there is an urgent need for vaccines to combat infectious and emerging infectious diseases. Although several autogenous inactivated vaccines have been developed and proved their protective efficacy under laboratory conditions,[60,61] none of them are commercially available. Legal barriers in the registration and approval process at the national FDA are one of the major factors contributing to the lack of access to vaccines for the Thai aquaculture industry, making the industry uncompetitive.[62] Strategic dialogue involving representative authorities, academia and industry stakeholders to identify a pathway for commercialisation of autogenous and licenced vaccines for Thai aquaculture industry is needed.

Australia: Australia represents an advanced economy ranked 13 in terms of GDP by the International Monetary Fund in 2020. The salmonid aquaculture industry in Tasmania is dominated by three companies and is substantial, worth $892 million (AU) in 2019, and was an early adopter of vaccination, first deploying vaccination against marine vibriosis in 1988 (https://dpipwe.tas.gov.au/Documents/AHL%20LabFact%20Fish%20Vaccines.pdf). The five currently registered and three permitted vaccines for salmonids are locally produced (Table 1). In contrast, the remainder of the fish farming industry bears a number of similarities with south east Asian neighbours, comprising a fragmented market of small and medium enterprise farmers producing a diversity of species in tropical and sub-tropical fresh and brackish water, mostly ponds. These small-scale producers are supported by local production of autogenous vaccines deployed under minor use permits, with veterinary stewardship (Table 1).[30] No antibiotics are registered for use in Australian aquaculture, but in some state jurisdictions, they may be prescribed off-label by a registered veterinarian and minor use permits are occasionally issued by the Australian Pesticides and Veterinary Medicines Authority (APVMA).[63] Antibiotic resistance has been reported in bacterial isolates from aquaculture settings in Australia.[64] However, the study conclusions that a relatively high prevalence of resistance within the sampled cohort is indicative of frequent off-label antibiotic use in Australian aquaculture and presents a threat to human health are not supported by the study data.[64] Firstly, the highest prevalence of resistance was to the B-lactams amoxicillin and ampicillin (54.8%) and to the first generation cephalosporin

TABLE 1 Availability of vaccines for commercial use in example countries

Pathogen	Vaccine type	Adjuvant: Route	Farmed species
Country: Australia			
Vibrio anguilarum (Anguillvac C)	Licensed killed whole cell	oil-emulsion: injection	Salmonids
Yersinia ruckeri (Yersinivac B)	Licensed killed whole cell	oil-emulsion: injection	Salmonids
Y. ruckeri, V. anguillarum, Aeromonas sp. (Tegovac)	Licensed killed whole cell	oil-emulsion: injection	Salmonids
Tasmanian Salmonid Rickettsia (Corrovac)	Licensed killed whole cell	oil-emulsion: injection	Salmonids
Salmon orthomyxovirus (Certovac)	Licensed inactivated	oil-emulsion: injection	Salmonids
Streptococcus iniae	Autogenous killed whole cell	oil-emulsion: injection	Barramundi (*L. calcarifer*)
Betanodavirus (RGNNV)	Recombinant protein	oil-emulsion: injection	Giant grouper (*E. lanceolatus*)
Lactococcus garvieae	Autogenous killed whole cell	oil-emulsion: injection	Rainbow trout (*O. mykiss*)
Photobacterium damselae ssp damselae	Autogenous killed whole cell	oil-emulsion: injection	Yellowtail kingfish (*S. lalandi*)
Country: Indonesia			
Streptococcus iniae	Killed whole cell	Immersion and injection	Tilapia (*Oreochromis niloticus*)
Streptococcus agalactiae	Killed whole cell	Immersion and injection	Tilapia (*Oreochromis niloticus*)
Streptococcus agalactiae serotype 1b	Killed whole cell	oil-emulsion: injection	Tilapia (*Oreochromis niloticus*)
Aeromonas hydrophila	Killed whole cell	Immersion and injection	All freshwater fish
Aeromonas hydrophila +Streptococcus agalactiae	Killed whole cell	Immersion and injection	Tilapia (*Oreochromis niloticus*)
Koi Herpesvirus	Attenuated vaccine	Immersion	Common carp (*Cyprinus carpio*) & Koi (*Cyprinus koi*)
Edwardsiella ictaluri	Killed whole cell	Immersion	Catfish (*Pangasianodon hypopthalmus*)
Iridovirus	Inactivated	oil-emulsion: injection	Grouper
V. campbelli 2J2 (antigen O) *V. fluvialis 24SK (antigen H)* *V. fluvialis 16G (antigen O)* *V. fluvialis 2SA (antigen H)*	Killed whole cell	Oral, immersion and injection	Humpback grouper (*Cromileptes altivelis*)
Streptococcus iniae strain jeju−45	Killed whole cells	Injection	Aquaculture
Streptococcus iniae, Lactococcus garviae	Inactivated	Oral and immersion	Tilapia (*Oreochromis niloticus*)
Country: Vietnam			
Edwardsiella ictaluri	Killed whole cell	Oil-emulsion: injection	Pangasius catfish (*Pangasianodon hypophthalmus*)
Aeromonas hydrophila +Edwardsiella ictaluri	Killed whole cell	Oil-emulsion: injection	Pangasius catfish (*Pangasianodon hypophthalmus*)
Streptococcus agalactiae	Killed whole cell	Oil-emulsion: injection	Tilapia
Streptococcus iniae	Killed whole cell	Oil-emulsion: injection	Tilapia
Streptococcus iniae +Streptococcus agalactiae	Killed whole cell	Oil-emulsion: injection	Tilapia

Note: Non-commercially available in Thailand as of June 2021.

cephalexin (41.4%). But, of 104 isolates tested in the study, 100 were Gram-negative bacteria that are poorly susceptible to penicillins and 22 of these were *Aeromonas* spp., which are innately resistant via low-temperature (30°C) de-repression of chromosomally expressed Β-lactamases.[65] The tests in the study were conducted at 30°C. The next highest prevalence of resistance was to erythromycin (47.1%), which is again unsurprising, given the long-known very low uptake of erythromycin across the Gram-negative bacterial outer membrane[66] While the authors acknowledge these issues in the discussion, along with the modest prevalence of tetracycline resistance, which they express surprise at given the regular use in Australian veterinary medicine, the stated conclusions ignore these points and also fail to acknowledge that several of the bacterial isolates included in the study are likely contaminants from terrestrial or human sources (*Staphylococcus* sp., *Micrococcus* and *Citrobacter*).[64] Whilst an up-to-date study of prevalence of AMR in Australian aquaculture is overdue, it cannot be concluded based on available data that the industry has a major problem. The access to vaccines by SME farmers in Australia via the local autogenous format and the relatively inexpensive and fast minor use permit process, overseen by the

APVMA, provides a useful regulatory and production example for alternatives to antibiotics where fragmented markets are unattractive to production or import of fully licensed and registered vaccines.

Chile: Chile is a middle-income country with a large aquaculture industry producing mostly salmonids, yielding 1,075,896 tonnes in 2020. In contrast to Norway where 222 kg antimicrobial was used to produce 1,375,307 tonnes in 2019 (160 mg antimicrobial per tonne),[23] Chilean producers used 379,600 kg antimicrobial in 2020 (353,000 mg per tonne), 2200 times more than Norway.[13] Moreover, vaccines in Chile are widely available to aquaculture.[67] It is therefore pertinent to explore the differences between the Norwegian and Chilean situation. In Norway, florfenicol (156 Kg) and oxolinic acid (66 kg) were used in 2019 with almost all prescriptions in hatchery fry and fingerlings pre-vaccination, a pattern that has been consistent during the last 7 seasons.[23] The importance of this cannot be understated as it demonstrates that vaccination strategies are effective in protecting salmon through marine grow out in Norway. Moreover, biomass in the hatchery is relatively low, so less antibiotic is required to treat infection that may occur before vaccination. On the other hand, in Chile in 2020, 97.6% of the antimicrobial use (370,490 kg) was during seawater grow out, comprising predominantly florfenicol (98.63%) with minor use of oxytetracycline, tiamulin and the novel macrolide tilmicosin.[13] Ninety two per cent of the antibiotic prescribed during marine grow out was for treatment of salmonid rickettsial septicaemia (SRS) caused by *Piscirickettsia salmonis*, a Gram-negative intracellular pathogen.[13,67,68] Vaccines have been available against SRS in Chile since 1999, but recent efficacy studies conducted by the Chilean government indicate poor long-term protection in salmon.[67,68] The intracellular nature of the infection may make successful vaccination challenging, with subunit, and live attenuated vaccines were less effective than killed bacterins.[67] Moreover, booster vaccination in seawater was also ineffective.[67] In spite of the availability of 32 different vaccines with an SRS component in Chilean aquaculture, the major driver of antibiotic use during grow out would appear to be the lack of an effective SRS vaccine that protects for the full farm cycle. Resolution of the degree of critical antigenic diversity amongst recent isolates from Chile would resolve whether blended autogenous vaccines might be more effective than mono-isolate generics in controlling SRS. It is also important to consider other potential drivers of the SRS problem in Chile. *P. salmonis* was isolated from salmon in Norway in the late 1980s[69] yet does not cause high incidence of invasive disease in farmed salmon in Norway. Seasonal water temperatures may be a factor in disease incidence, while summer water temperatures are similar between Puerto Montt and the mid-Norwegian Atlantic coast (16–17°C max), the winter temperatures in Norway are substantially lower (4–6°C vs 10–11°C). Most Rickettsias are transmitted via arthropod vectors, and although no vector for *P. salmonis* has been found, it is able to grow well in insect cell culture[70]; therefore, conditions suitable for high vector prevalence may also play a role. Indeed, fish were observed feeding on zooplankton when outbreaks occurred in Norway.[69] Outbreaks in Norway followed phytoplankton blooms in the Autumn,[71] and it is likely that the high concentration of salmon farms in the Puerto Montt region of Chile[72] and associated eutrophication[73] contributes to the higher incidence and severity of disease. A holistic veterinary approach to management of the SRS problem which includes identifying and addressing environmental and husbandry risk factors appears warranted at an industry and cage level. That disease in Norway occurred predominantly in overstocked smolt pens reinforces the importance of corrective actions to address husbandry drivers of disease.[69] In addition to these, improved vaccines that consider potential diversity and intracellular nature of the pathogen may assist.

1.3 | Current commercial vaccine efficacy

Commercial licensed, registered vaccines have been used for farmed fish in many countries. However, systemic assessment of these vaccines' efficacies against the diversity of local strains in the field is still largely poorly documented. However, a number of studies provide evidence of inadequate protection of commercial vaccines in field application due to the differences between vaccine and local strains. These include red sea bream iridovirus (RSIV) vs. infectious spleen and kidney necrosis virus (ISKNV) in an Asian seabass farm in Vietnam[74] and *Streptococcus iniae* serotype I and *S. iniae* serotype II in a rainbow trout farm in Israel.[75] Indeed, serological diversity also resulted in vaccine escape outbreaks of Streptococcosis caused by *S. iniae* in Australia, where fish were vaccinated with a commercial autogenous vaccine highlighting the importance of the inclusion of the correct antigens and critical nature of polysaccharide antigens in vaccine protection.[30,76,77] The importance of polysaccharide antigens to protective efficacy of vaccines for fish is critical in both Gram-positive and Gram-negative bacteria where capsular polysaccharide and LPS O-antigen are the protective components in many killed bacterins, including *Listonella anguillarum*,[78-83] *Vibrio ordalii*,[84,85] *Yersinia ruckeri*,[86] in addition to *S. iniae* [87] and *S. agalactiae*.[88,89] There is scope for quite high serologically relevant diversity via mutational and recombinational changes in the complex biosynthesis machinery for LPS O-antigen[37] and capsular polysaccharide.[77] With a few notable exceptions, serological diversity is rarely considered in scientific fish vaccination trials, where the vast majority of challenges are performed using the vaccine strain. Where multi-serotype models have been employed in laboratory challenges, low cross-serotype protection is generally found.[87-92] In this regard, auto-vaccines produced from the local strains should have a critical advantage over commercial registered vaccines.

1.4 | Tentative steps towards antimicrobial reduction in aquaculture through auto-vaccines

We present a tentative needs analysis towards enabling autogenous vaccination as part of a holistic animal health programme for finfish aquaculture in developing countries (Figure 1). There are clear needs for improved knowledge, infrastructure and bureaucracy to transition from the current situation into a more proactive, evidence-based future for prevention and control of aquatic diseases (Figure 1). Building farmer trust and confidence will be critical to successful change. Here, the role of the service extension worker, aquatic health professional and veterinarian in each region will be of foremost importance. Trusted and secured platforms for collection and storage of data are required for farmers to be transparent and share outbreak metadata without the fear of negative impacts on their business or reputation. Trust amongst farmers is more easily earned where data supplied are returned as information that can be used by the stakeholder in self-implemented practices—a bottom up self-help model as opposed to top-down approaches.[93,94] Equity of access to trained professionals for sample collection with standardised protocols is key for good disease management and diagnosis (Figure 1). Where there remain difficulties in obtaining early outbreak reports and correct field/laboratory diagnosis, there will be difficulties in achieving high success rates with auto-vaccination. Some risks will remain that vaccines could be formulated against organisms that are not drivers of the disease expression but opportunist pathogens that exploit animals that are compromised by poor environment or malnourishment.[95,96] For evidence-based interventions, standardised and high-resolution pathogen identification and typing are necessary (Figure 1). A documented pathway from sample collection to locally owned biobank of pure bacterial isolates, including systematic antimicrobial sensitivity testing (AST) by local, regional or national laboratories following international standards, should be implemented. Such information is critical to inform farmers on the best course of action for biosecurity measures, feed/water management, guided antibiotic use or emergency harvest during an outbreak (Figure 1). High-resolution typing is more easily addressed. Advances in sequencing technology and reduction in cost enable inclusion of sequencing in the diagnostic and documentation process. For example, Nanopore instruments are small and can be used directly in the field.[97] They have demonstrated capability to rapidly and accurately generate high-resolution typing information from bacterial pathogens in near real time.[98] Sequence type information might inform local biosecurity pathways, while serotype is essential for autogenous vaccine formulation. Long read Nanopore sequencing can also be used to detect antimicrobial resistance genes and, with sufficient 'ground-truthing' against phenotype, potentially be used to inform targeted prophylaxis directly from sequence reads in real-time.[99] Of course, for vaccination programmes to be effective they should be implemented in hatcheries or nurseries before dissemination of seeds to farmers, which will require some consolidation and transition in many countries. Gradual change of practices is in progress with adoption of specific pathogen free (SPF) seed production in the regional shrimp industry, but it is yet to be applied in other less valuable locally consumed species such as tilapia, carp and catfish. These pathways should be supported in a clear regulatory framework allowing flexibility of autogenous format with informed permission to produce and sell auto-vaccines to hatcheries supplying farms affected by the same strains.

Successful vaccination programmes have several features that will need to be resolved within each farming context. Vaccines are not silver bullets for disease control but can be part of the solution. Aquatic veterinarians/health professionals have the required skill set to assist in addressing each of the co-contributory environmental risks which drive disease expression. These include the following: improved parasite surveillance and control; better diagnostic capacity; implementation of improved biosecurity to reduce the risk of pathogen introduction and spread; reduction of pollutant exposure via water and diets coupled to improved water quality monitoring and response and correction to aberrant changes; improved nutrition; improved handling and farming practices; consideration of alternative treatments to antibiotics; and use of genetic improvement programmes towards disease resilient stock all need to be incorporated within a vaccination programme to foster the best chance of success in a One Health framework for sustainable aquaculture.[11,100] Equally important is a regulatory and compliance framework that limits use of antibiotics. For example, a reduction in permitted MRL would extend with-holding periods post-treatment. Coupled with regular product sampling for compliance, this would change the decision-making by farmers about application of treatments to large fish as they approach market size, favouring earlier intervention strategies through husbandry and vaccination.

2 | CONCLUDING REMARKS

In summary, overuse and misuse of antibiotics in aquaculture in LMIC where growth of the industry is fastest and essential for nutritional security are challenging but solvable problems, evidenced by the rapid near-elimination of antibiotic use during the early growth of the salmon industry in Norway. We acknowledge the different starting points between Norway of the late 1980s and most of the aquaculture-dependent LMIC in 2021 in terms of governance, education base, finance, population and associated environmental degradation. We identify equity of access to aquatic animal health professionals, farmer education and acceptance of vaccine technology along with a harmonised simple regulatory framework as the most important enabling factors. The contrast between ease of availability of antibiotics and the difficulty in registering vaccines was also noted. We re-iterate that there are no major technological issues that need to be resolved. Use of locally produced killed, autogenous vaccines has a number of advantages. These include the following: flexibility to re-formulate and produce new vaccines for each crop as necessary in response to strain evolution; identification and high-resolution typing of bacterial isolates from fish farms is becoming easier, faster and cheaper through developments in sequencing technology and bioinformatics; no major restrictions on intellectual property as methods for growth and inactivation of locally isolated bacteria are in the public domain or are obvious to a skilled practitioner; removal of perceived transboundary biosecurity risk through import/export of biological material; retention of biological resources, skilled human capital and economic activity in-country will be beneficial in developing countries and will not widen the gap between low and high-income economies. Moreover, timely use of autogenous vaccination in LMIC may facilitate early containment of novel virulent serotypes arising at accelerated rate in tropical freshwater environments. We foresee some potential inertia in regulatory and policy acceptance of autogenous vaccines, particularly around extension of use to multiple sites. Although we propose the autogenous route as one of the innovative veterinary solutions for emerging economies, it is possible that established companies may find the strategy alarming as dissemination into established high-value markets such as salmon could threaten existing business practices and market share. Our experience in Australian aquaculture supports that auto-vaccines can co-exist with fully licensed products and allow the benefits of vaccination to flow to small-scale aquaculture producers that would otherwise be unsupported. There is an indispensable role for carefully crafted government policy that enables competition, and we encourage an international dialogue around harmonisation of a simple and clear framework to permit safe, locally produced autogenous formulations. Finally, we accept that autogenous vaccination is not a panacea, but it is a very useful tool for some diseases in some species, set within a stakeholder education framework for better husbandry and environmental practice, aligned with the 'One Health' paradigm for aquaculture.[11,100] In the face of a global antimicrobial resistance crisis, a robust discussion is urged in favour of autogenous vaccination as a fast and relatively simple intermediate technology that can be implemented locally to cut antibiotic use and break the chain of AMR promotion in developing nation aquaculture.

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Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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