TYPOLOGY OF INTERVENTIONS TO REDUCE USE OF ANTIMICROBIALS IN AQUACULTURE SYSTEMS IN LOW- AND MIDDLE- INCOME COUNTRIES

Report, December 2019

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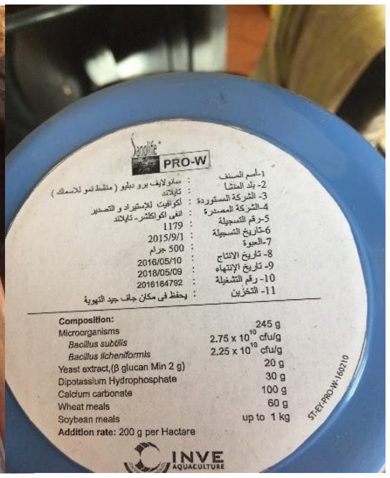

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EXECUTIVE SUMMARY

Scientific evidence from a landmark study recently published in the Lancet Report shows that food systems must radically change if we are to avoid potentially catastrophic effects on our collective health and irreparable damage to the planet (Willett et al. 2019). Food systems — encompassing all activities from inputs, production, harvesting, processing, distribution, marketing, consumption to waste management supported by relevant services, governance and policy — are complex and solutions must be creative to supply affordable, safe, and nutrient-rich food from land, freshwater and ocean ecosystems in a sustainable manner.

Fish plays a critical role in this mission. Fish provide essential fatty acids and key micronutrients such as vitamins A and B12, iron, calcium, zinc and iodine, as well as animal protein. More than 50% of the fish that we consume globally is presently coming from aquaculture.

Aquaculture is the fastest growing food sector in Low and Middle Income Countries (LMICs). Increased production has been achieved through intensification of aquaculture systems while neglecting farm-level biosecurity and aquatic health management. As a consequence, indiscriminate antimicrobial use (AMU) to treat or prevent disease and increase productivity is common (Alday-Sanz et al. 2012; Rico et al. 2012), and often compensates for management and husbandry deficiencies. Regulation and enforcement of the responsible use of antimicrobials is often inefficient or absent (Bondad-Reantaso, Arthur, and Subasinghe 2012). Further, there is no comprehensive framework to understand existing interventions to reduce AMU in the aquaculture sector. Focusing on aquaculture systems in LMICs, the aim of this study was to provide insights into interventions and strategies applied that can reduce AMU. The objectives were 1) to conduct a typology analysis of past, current, and planned strategies and interventions to tackle AMU, 2) to provide an analytic framework of interventions in the field, 3) to provide an overview of the policy landscape with regards to AMU/AMR.

Professionals with knowledge and/or experience in the design and implementation of such interventions in LMICs in Asia and Africa were interviewed to gather information on interventions, strategies, and the policy landscape. Interventions were framed according to the AMU goal of the interventions, namely, (i) promoting responsible and/or reduced AMU, (ii) providing commercial alternatives to AM, and (iii) removing the original cause of the problem, e.g., addressing animal health management. Subsequently, relevant variables representing the characteristics of an intervention and implementation were identified and combined in a multidimensional typology process. Seven types of interventions were identified, namely i) National Action Plans and National Fish Health Management strategies, ii) national legislation and regulatory frameworks, iii) market-driven strategies, iv) technology and product solutions, v) on farm management, vi) learning and raising awareness, and vii) activities with co-benefits on AM reduction and aquatic health. Further themes emerged in the discussions including the situation and perception of AMU, drivers of AMU and challenges for aquatic health and aquaculture systems. Consequently, drivers and pathways of AMU were mapped and linked to the typology.

Characterisation of the types revealed common aspects across countries. Several legislative and regulatory frameworks for aquatic medicinal products were described but poor enforcement was reported to be common. Inspection and control appeared to be often limited to market, and in particular export, oriented commodities resulting in reduced AMU and respecting of withdrawal periods. Vietnam was mentioned as an example of a country engaging in the NAP activities specific for aquaculture, while other countries were described to be at earlier stages in the process, working with international organisations. Other interventions such as technological and product solutions as alternatives to AM were described to be widely popular, despite the certainty on the quality of products. Further, on farm management interventions and learning, awareness raising and attitude change were commonly locally implemented engaging a wide variety of stakeholders.

This study provides an overview and typology of existing strategies and interventions targeting AMU in aquaculture systems in LMICs. This forms the basis for future work to evaluate AMR-sensitive interventions that promote responsible AMU, and to inform the design and implementation of future interventions.

INTRODUCTION

Aquaculture is the fastest growing food sector in Low and Middle Income Countries (LMICs), driven by an increasing demand for affordable protein and trade opportunities. It produces more than half of the world's seafood for consumption and is growing globally at a rate of 6% per year since 2001. Seven of the top ten aquaculture producers are LMICs; their contribution to the global trade of aquaculture is growing (FAO 2018). In the last decades, the rise of aquaculture has responded to the growing demand for fish and fish products (Troell et al. 2014). Further, despite the importance for human nutrition, aquatic products are neglected in the food security discourse and their nutritional potential beyond the protein value, with unsaturated fatty acids and micronutrients is often undervalued (Béné et al. 2016).

Global trade in live aquatic animals and intensification of aquaculture are important drivers for the emergence and spread of infectious diseases. Increased production has been achieved through intensification of aquaculture systems, where animals are farmed outside their natural physiological, biological and ecological boundaries. This has often led to increased occurrence of diseases and crop loss (Leung and Bates 2013; Hall et al. 2011). As a consequence, indiscriminate antimicrobial use (AMU) to treat or prevent disease and increase productivity is common, and often compensates for management and husbandry deficiencies (Bondad-Reantaso, Arthur, and Subasinghe 2012).

The main driver of AMR is described to be the misuse of AM (Henriksson, Troell, and Rico 2015; Rico et al. 2013). The use of AM in aquaculture systems in LMICs is thought to be high, but levels are unknown due to a dearth of surveillance systems (Brugere, Onuigbo, and Morgan 2017). In addition, AM are usually applied with feed, potentially leading to excretion of non-absorbed chemicals from fish into the water, or direct contamination of water if feed is not consumed. Because aquatic environments also contain diverse bacteria populations, risks are created for AMR development and exchange of plasmid between resistant and non-resistant bacteria. Furthermore, aquaculture facilities are often open systems interconnected with the natural water environment through irrigation or flow of water, producing wastewater discharges into them. The use of chemicals and biological products in these systems has the potential to impact the surrounding ecosystems (Rico et al. 2012; Done, Venkatesan, and Halden 2015) as presence of residues has been evidenced in different studies (Le and Munekage 2004; Xue et al. 2013).

Despite the risk for AMR emergence and importance for food security, aquaculture systems remain neglected in terms of health research and management compared to other terrestrial productive systems. Further, the distribution of aquaculture production and development worldwide is uneven generating regional risks. While Asia accounted for almost 90% of aquaculture production in 2016 (of which 60% was produced by China), Africa represented 2.5%, of which 1.7% was produced by Egypt alone (FAO 2018). In LMICs, regulation and enforcement for the responsible use of antimicrobials is often inefficient or absent and monitoring or surveillance systems for AMR and AMU are often absent or not systematically implemented. Further, there is no comprehensive framework to understand existing interventions that can lead to AMU reduction in the sector. This study aimed to provide insights into interventions and strategies applied in aquaculture systems in LMICs that can reduce the use of AM. The objectives of this study were 1) to conduct a typology analysis of past, current, and planned strategies and interventions to tackle, 2) to provide an analytic framework of interventions in the field, 3) to provide an overview of the policy landscape with regards to AMU.

METHODS

General overview

An eight-step process was used to develop the typology of interventions tackling AMU in aquaculture in LMICs (Figure 1). Following an initial review and conceptualisation step, semi-structured interviews were conducted with aquaculture professionals with experience in LMICs to obtain information about interventions and strategies applied in aquaculture systems that can reduce the use of AMs as well as evidence of their impact. The interview data were analysed and used to build iteratively a multi-dimensional typology framework for these interventions. The details of this process are described in the following sections.

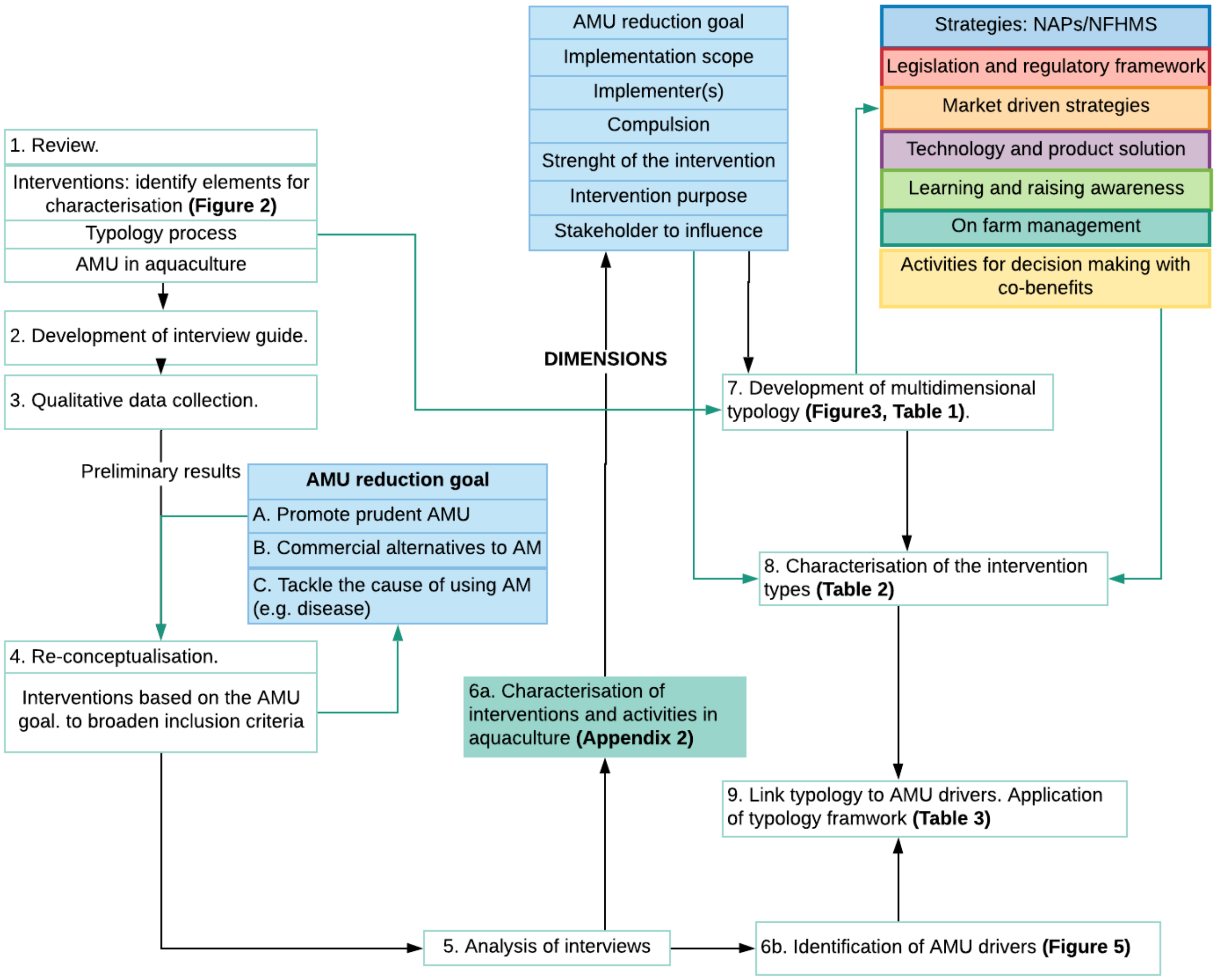

Figure 1. Steps used to develop the typology. AMU=Antimicrobial use; NAP=National Action Plan; NFHMS= =National Fish Health Management Strategies,

Step 1. Review

We defined the term "intervention" as any formal action designed to address purposefully a challenge with the aim of obtaining a desired change in the system. We reviewed different existing frameworks to identify relevant elements for the interviews. The following three approaches were used:

1. International Classification of Health Interventions (ICHI, https://mitel.dimi.uniud.it/ichi/docs/) that defines intervention as '*an act performed for, with or on behalf of a person or a population whose purpose is to assess, improve, maintain, promote or modify health, functioning or health conditions*' and uses

three elements to characterise an intervention, namely target population, action, and means of implementation.

2. The Nuffield ladder of interventions that categorises interventions by virtue of their relative intrusiveness in people's lives ranging from complete freedom of choice to regulations banning or restricting choice (Nuffield Council on Bioethics 2007)
3. The application of choice and non-choice based interventions to animal health compensation and biosecurity (Barnes et al. 2015) to consider the strength of intervention and degree of intrusiveness and the potential for behavioural interventions and implementation features.

The study of these frameworks resulted in the definition of the variables shown in Figure 2, namely

- Interventions (action)
- Target or stakeholder to influence
- Purpose of the intervention
- Implementer or stakeholder involved
- Means, method of implementation or delivery mechanism
- Degree of compulsion, and
- Strength of the interventions

These variables formed the basis for the development of the interview guide. In addition, the literature review included search on methods to conduct a typology analysis and documentation on AMU in aquaculture.

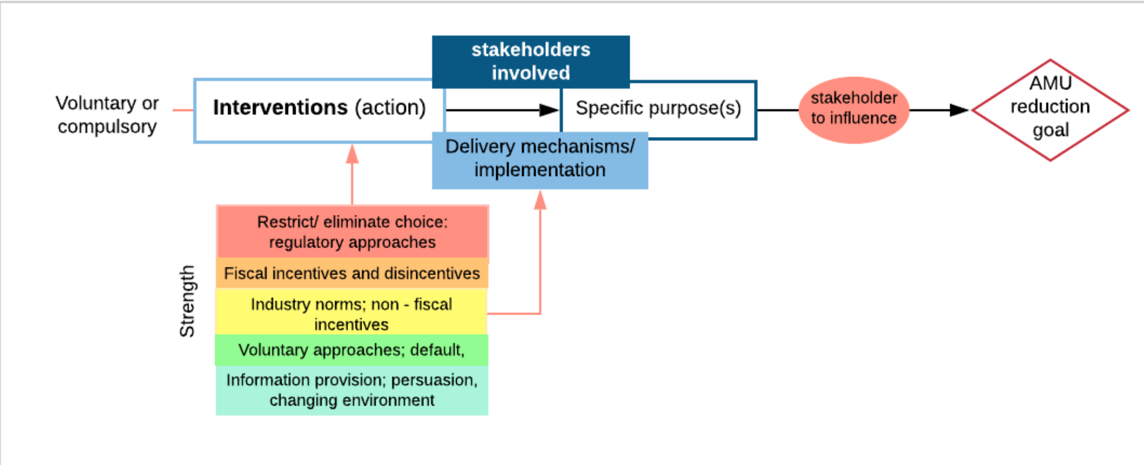

Figure 2. Variables to characterise an intervention

Steps 2 and 3. Development of the interview guide and data collection

The interview guide (Appendix 1) aimed to capture potential classifying elements and understand the policy context that can influence the implementation. Initial scoping discussions with stakeholders informed the selection of case countries based on the aquaculture development stage, role of the sector, perceived AMU levels, initiatives against AMR and access of information, while ensuring a good range of representation of different aquaculture systems. The selection of professionals was purposive and we followed a snowball process. First, established collaborators in international and academic institutions with experience in the sector were contacted and interviewed. In a second step, other national experts in public and private institutions in Egypt, Zambia, Uganda, Kenya, Bangladesh, India and Vietnam were interviewed based on recommendations made by our contacts. Apart from talking about the experience in their countries, the interviewees provided information about other countries and trends based on their experiences. Interviews were conducted in English using online meeting applications and hand-written notes were taken throughout the process. Discussions covered the policy landscape in each setting, and past, current and future activities to address the AMU challenge. Further, during the interview process different themes emerged, including the level of AMU settings, perceived drivers of AMU and challenges for aquatic health and management, and for aquaculture in general. Further, participants shared relevant documents and sources of information discussed during the interview.

Step 4. Re-conceptualisation

The initial aim was to obtain information solely on interventions to reduce AMU. In the light of the preliminary results, the scope was expanded to consider information on any activities, actions or strategies, occurring in the systems that can lead to a reduction of use of AM in aquaculture systems as a co-benefit. Accordingly, these included activities (A) designed to achieve prudent use, whose main goal is to primarily address AMU; this group includes, specific regulation for AM sales; (B) providing commercial alternatives to AM, aiming for an economic gain while promoting health; (C) preventing disease by addressing management and low productivity associated with production management.

Steps 5 and 6. Data editing, analytic process and framework development

Interview notes on interventions were screened to identify suitable variables (or dimensions). These variables were the action; target or stakeholder to influence; purpose of the intervention, implementer and stakeholders involved; means, method of implementation or delivery mechanism; degree of compulsion and strength of the interventions; impact; and monitoring and evaluation. For each variable, a set of categories was identified based on the information collected. Appendix 2 shows an overview diagram used to identify some key variables from the information obtained. To develop the typology, variables were considered with enough information to generate discrete groups, and characterise the intervention. Simultaneously, information on emerged themes was mapped as drivers and pathways of AMU.

Steps 7 to 9. Typology analysis, characterisation and application.

Figure 3 outlines the process to develop the intervention types. The types were obtained by combining the categories of the different variables represented as each column, a component to characterise an intervention. Based on the information obtained, links were established between the components, to finally generate the types. Information on perception of use, drivers and pathways to AMU from interviews illustrated the background of the system and helped to identify "*where to intervene in the system*"; this differed by context. Finally this analytic framework was applied on the strategies obtained to characterise the interventions identified.

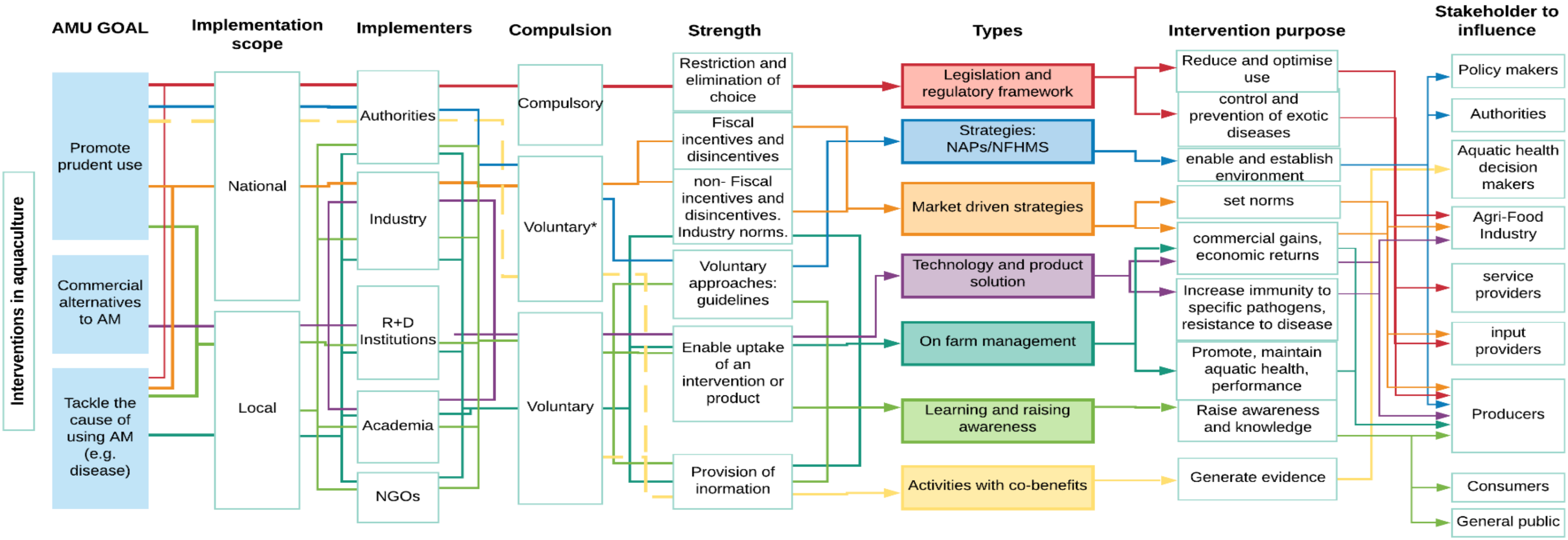

Figure 3. Development of the multidimensional typology for interventions to tackle AMU in aquaculture in LMICs. Each column represents the different variables or dimensions in the typology, with the specific categories.

RESULTS

Interviews conducted and summary of interventions

A total of 17 interviews were conducted with different professionals from academia, international organisations, government and the private sector in UK, Egypt, Uganda, Kenya, Zambia, Bangladesh India and Vietnam. Table 1 outlines the types of interventions identified and their respective profiles.

Table 1. Summary of interventions types based on the variables considered for the analysis. NAP=National Action Plan.

Types	AMU goal	Implementer	Implementation scope	Compulsion	Strength	Purpose	Stakeholder to influence(target)
Legislative and Regulatory frameworks	Prudent use Tackle cause of AMU	Authorities	National	Compulsory	Restriction or elimination of choice	Reduce and optimise use Control and prevention of disease	Agri-food industry Service providers Input providers Producers
NAPs, National Fish Health Management strategy	Prudent use	Authorities	National*	Voluntary	Voluntary guidelines	Enable and establish environment	Policy makers authorities Producers
Market driven interventions	Prudent use Tackle cause of AMU	Industry	National*	Voluntary*	Incentives, disincentives	Set norms Promote public health Economic returns	Agri-food industry Input providers Producers
Technology and product solutions	Commercial alternatives to AM	Industry R+D instit. Academia	Local	Voluntary	Enable the uptake of a product or technology	Commercial gains. Economic returns Increase immunity or resistance to disease	Agri-Food industry Producers
Learning and awareness raising – behavioural interventions	Prudent use Tackle cause of AMU	Authorities Industry R+D instit. Academia NGOs	Local	Voluntary	Voluntary approaches Enable uptake Provision of information	Provide knowledge. Raise awareness. Attitude change	Producers Consumers General public
On farm management interventions	Tackle cause of AMU	Authorities Industry R+D instit. Academia NGO	Local	Voluntary	Non-fiscal incentives Voluntary activities Enable uptake Provision of information	Commercial gains. Economic returns (farmer) Promote, maintain aquatic health	Producers
Activities with co-benefits for AMU and AMR	Prudent use Tackle cause of AMU	Authorities R+D instit.	National/ Local	Voluntary*	Voluntary activities Provision of information	Generate evidence	Aquatic health decision and policy makers

Characterisation of types in the multi-dimensional typology

Table 2 shows the application of the typology framework to characterise the different examples obtained in the interviews. Further information on each type - collected during the interviews and in the literature review - is provided in the following sections.

Table 2. Typology of interventions in aquaculture to reduce antimicrobial use in low and middle income countries. SPF=specific pathogen free. GIFT=Genetically Improved Farmed Tilapia. BMP=Best Management Practice.

Types	Action or intervention	AMU goal	Implementation Scope	Implementer	Strength	Compulsion	Purpose	Stakeholder to influence	Delivery mechanism/ implementation
National strategies	NAPs, National Fish Health Management Strategy.	1	National	Authorities	2	V*	Establish and enable environment for AMR control	Governments/ authorities	
National Legislation and Regulatory framework: Act > Law > Regulation	AM list of banned products; dose (e.g. in feed), withdrawal periods	1	National	Authorities (inspectors)	5	C	Restrict, Control use	Drug sellers; Producers	
	Prophylactic health products						Regulate use		
	Role of veterinarian, licensing.						Define role and	Service provider, Drug seller	
	Control of diseases	3					Import	Importers of seed	
Market driven	Export requirements, demands from industry	1	National	Authorities	3	V*	Food safety in importer countries;	Commercial exporters	
	Meta-governance arrangements – GSSI, ISEAL, AESAN GAP	3	International		3		Strengthen effectiveness of standards/ harmonise		
	Certification standards		National	Authorities; industry	3		Improve product quality, benchmarking.	Commercial exporters	
	Enable exports markets		National	Authorities	2		Economy	Commercial exporters	
Technology and product solutions	Vaccines	2	Local	various	2	V	Prevent and control disease	Producers	Enable the choice of uptaking a product or technology
	Feed additives, probiotics, prebiotics			Private sector			Prophylaxis; economic gains		
Learning and raising awareness (behaviour)	Community engagement	1 3	Local	Various	1	V	Promoting behaviour and attitude change	Community	Provision of information: potential use of nudges, enhancements, participation: peer comparison, champions, role models, social media.
	Media campaign		National	Media				Public	
	Awareness campaign		Local; National	R+D, NGOs, Authorities, private sector					
	Training	3	local					Producers, input providers	
On farm management	Best management practices, uptake of technology SPF seed. GIFT	3	Local	R+D, Academia, private sector	2	V	Promoting uptake and adoption of BMPs. Biosecurity	Producers	Knowledge provision
	Environmental interventions						Performance		
	Husbandry interventions						Biosecurity. Performance		
Activities with co-benefits for AMU/AMR	AMR/AMU surveillance	1	National	Authorities	3/4	V	Generate evidence	Aquaculture decision and policy makers	
	Residues surveillance			Authorities					
	Disease surveillance	3		National, R+D, Academia					
	Decision making tools	3	Local; project	Academia	1/3				

AMU Goal: **1:** Promote prudent use by limiting and controlling use; **2:** Provide alternatives to AM (products and technology); **3:** Tackle causes of AMU: disease, lower productivity, poor management practices. **Strength of interventions: 1:** information provision; persuasion; changing environment; **2**: voluntary approaches, enable the uptake of a product or intervention; **3**: industry norms, non-fiscal incentives or disincentives. **4:** Fiscal incentives or disincentives. **5:** Restriction or elimination of choice by regulatory approaches.

Legislative and regulatory frameworks

Interviewees from all countries mentioned the existence of some legislative and regulatory framework that refers to aquaculture medicinal products within the Animal Health or Fisheries Acts, and regulates the use, implemented by authorities (extension services and inspectors). Common aspects reported were the existence of a list of forbidden AM products and inspection of input providers, pharmacies and production plants. Problems of enforcing the regulation were mentioned; sometimes due to lack of human resources or lack of stringent consequences when inspection is applied. Quality of drugs was mentioned to be a problem, concerning pharmacies or distributors of products. Recent studies in Vietnam (Phu et al, Than et al) showed that commercialised products are of poor quality, and do not match the active ingredient referred. Other regulations mentioned referred to the control of the seed imports in the countries to minimise the risk of epizootic diseases.

National Action Plans (NAPs), National Fish Health Management Strategy (NFHMS)

The aim of NAPs for AMR and other national fish health strategies is to establish and enable the regulation and pro-active action towards the control of AMR. Among the countries considered, Vietnam presented the most advanced plan for targeted interventions that included surveillance activities, awareness raising, and enhancement of One Health governance. Other countries such as Egypt or Zambia were described to be undergoing the first stages towards interventions to mitigate AMR with the assistance of FAO, who provides training and planning for the competent authorities in the country to take responsibility and assure a sustainable implementation. These activities with stakeholders were described to be oriented to address primarily aquatic health following a holistic and systems approach tackling the root of the problem of AMU and AMR. They often related to management of aquatic health. Other countries such as Bangladesh were reported to be developing national fish health strategies, where interventions regarding use of aquatic medicinal products is a component of the plan.

Market driven interventions

Certification standards were described to have driven AMU reduction in Asian countries. Their main aim was said to establish a benchmark for sustainable production; AMU was included as a section. Different international labels, and national labels (e.g. VIETGAP) were mentioned, with involvement of industry and other national stakeholders. Accordingly, different stakeholders in the Agri-food business, such as importing retailers or exporting stakeholders in the value chain, demand standards for producers to comply with that are set up by third-party companies. The effect of export and market driven activities has been documented, analysing the data from the EU's Rapid Alert System for Food and Feed (RASFF) regarding aquaculture products (Newton et al. 2019).

Technology and product solutions

Different products were mentioned to be used in aquaculture systems as prophylactic use. The most common products listed were probiotics and vaccines. Probiotics were described to be widely commercialised by private companies and used extensively in commercial systems with distribution through pharmacies, drug sellers or distributors or at the farm level. However, evidence about the effectiveness of these products is unknown. The IMAQulate project, "*Evaluating Costs and Benefits of Prophylactic Health Products (PHPs) and Novel Alternatives on Smallholder Aquaculture Farmers in Asia and Africa"* led by the University of Stirling implemented a randomised control trial in India and Kenya to evaluate the cost and benefits of these prophylactic products as well as their quality. Preliminary results indicated ineffective active ingredient concentrations, contamination with bacteria pathogenic to humans, fraudulent inclusion of antibiotics and presence of antimicrobial resistance genes. Further, many products lacked credibility regarding their mode of action and efficacy claims. In addition, they identified a lack of effective sampling approaches as part of emergent regulatory efforts resulting in lack of detection of some problem-products in screening efforts whilst the economic burden of poor quality assurance and unjustified claims is likely to fall most heavily on small-holders. The IMAQulate project collaborators are following up with a project in Bangladesh, applying a decision tool developed by them.

The use of vaccines was mentioned in several interviews as the best method proven to decrease use of AM to very low levels. Examples discussed were the case of Norway and UK, characterised by a very high use of antibiotics in 1970s and 1980s. After implementation of vaccination, use levels of AB drugs declined while production increased (Asche 2008). However, vaccination in these scenarios was combined with other interventions that might have contributed to this success and data on the impact often only accounts for effect of vaccination. These others interventions were the availability and access to diagnostics, industry support and a regulatory framework combined with successful enforcement. The use of vaccines was mentioned in Egypt and Vietnam for diseases of catfish and tilapia; development is ongoing. On the other side, some respondents expressed scepticism, arguing that vaccines only target one microorganism, whereas mortalities in water systems can be the result of a complex combination of different microbial agents. Moreover, they observed that vaccines increase the production costs substantially, and it is unknown whether farmers would be willing to make such investment, or whether they can afford it. Currently, in countries like Vietnam, costs of AB in catfish were reported to be 0.02$/kg, normally adding 1kg/30 tons of fish. The cost of some vaccines was reported to start at 0.02$ per fish thus making vaccine use more costly than AB use for the producer. Finally, they expressed concerns on the regulation of vaccination in LMICs that are characterised by a wide variety of systems in terms of species, sizes and levels of commercialisation, and often face problems of enforcement (as described above). However, interviewees believed that vaccination might be feasible in more homogeneous production systems with support from the private sector if it is affordable for the producer.

Learning, awareness raising and behavioural interventions

Two forms of such interventions were described, namely 1) stand-alone instructive activities including information and knowledge provision, capacity building, training, and awareness campaigns, and 2) cross-cutting delivery mechanisms in the other interventions to enhance implementation and uptake.

In June of 2019, WorldFish launched an awareness raising campaign in Bangladesh among the public regarding AMU/AMR in aquaculture systems in collaboration with the University of Exeter. The intervention, previously informed by a survey and investigation of effective implementation, was broadcasted in different media platforms. Engagement and responses in social media were monitored, using analytical parameters including views, likes and comments. While such interventions were thought to have potential, there were also concerns about negative repercussions with the involvement of media in topics that can create food scares. One such example is the impact of EU media on Asian seafood markets (Newton et al. 2019).

Training activities were found in all countries, mainly to address aquatic management and in the sub-Saharan African countries also to engage farmers into aquaculture activities. In addition, behavioural influences were described. Across all countries, respondents highlighted the effect of who delivers the information to engage producers into practices, programmes, and technologies. Producers presenting positive production performance were described to be role models and were used as ambassadors for other peers, while service and input providers acted as distributors of information between different producers. Further, the use of group messaging networks via mobile devices was described among participants to exchange information like market prices of fish with the potential of norm setting.

On farm management interventions: Best Management Practices

On farm interventions were described as critical to prevent disease, maintain aquatic health and profitability of activities. In Egypt, the impact of best management practices (BMP) was assessed (Dickson et al. 2016), involving the training of farmers that were compared to a control group. These types of interventions were aligned with the introduction of global certification standards planned to improve environmental practices. The study showed how variable costs (e.g. feed) in adopters of BMP were considerably lower and net profits were significantly higher. In Vietnam, despite the high adoption of certification standards by commercial exporters, input providers described that BMP are considered as a burden among some producers and "not worth the effort".

Activities with co-benefits for AMU and AMR: interventions to generate evidence

Surveillance

The aim of surveillance systems is to generate evidence to inform interventions. In the context of AMU in aquaculture, surveillance information on AMR, AMU and/or residues can inform the design of interventions to reduce AMU and AMR. Surveillance of AMU, AMR and residues has been enhanced by NAPs in countries where such plans have been implemented. Among the interviewed LMICs countries, Vietnam was found to have the most formal surveillance system, strengthened as a result of the NAP. However, the system was said to have been implemented on an ad hoc basis in commercial commodities, often relying on samples sent to the authorities by farmers in situation of disease.

One of the critical points was described to be the need of surveillance protocols for AMU and AMR in an integrated manner across animal, human and environment systems. To respond to this, the Flemind Fund, an UK aid programme, aims to enhance surveillance systems, by developing common protocols for all food production sectors, to generate evidence for decision maker following a One Health approach, integrating human and animal resources. This is subsequently aimed to be applied in more than twenty countries in Africa and Asia.

Decision tool projects

Different projects were described to develop and apply tools for decision makers and different levels of the system. One was the "Risk-based pedigree-analysis for regulation of prophylactic aquaculture health products and improved smallholder health management in Bangladesh". Following up from evidence generated in the IMAQulate in South Asia on the quality of prophylactic aquaculture health products, this project has developed a risk analysis tool to assist users in identifying high risk products based on different indicators. The tool, implemented in Bangladesh in shrimp and pangasius producers, aims to raise awareness among stakeholders and support uptake of effective regulatory frameworks at the national level that can lead to more effective health management in aquatic small-holder systems.

Perceived use of AM in aquaculture systems

All respondents acknowledged the challenge of AMR in aquaculture systems due to inadequate or indiscriminate use of products and complexity of the ecological systems. However, concerns and priorities varied in different countries. In Vietnam, the extensive use of AMs in different production systems, also reported in studies (e.g. Rico et al. 2013), was highlighted by respondents (both, researchers and service providers) and described as usually being indiscriminate. In exporting commodities, in which use is more controlled, withdrawal periods were said to be respected, but prophylactic use common throughout the production cycle. Other concerns stated were the frequent use of AB for humans (e.g. in Vietnam, cefotaxime, a third generation cephalosporine; quinolones, etc.); inappropriate the dosage of AB (*"usually based on experience, but producers double the dose if AB ineffective"*) and the quality of products sold as also found by Tran et al(2018). In contrast, respondents from Uganda, Zambia and Kenya did not perceive AMU as a very significant challenge yet, as the aquaculture sector in these countries was described to be under-developed in comparison to Asian countries, and farmers did not seem to access the drug supply chain as much as for terrestrial animals. Yet still, due to the growth and intensification, it was reported as an increasing problem. For instance in Uganda, the use of AM was believed to be of ~10% in grow-out ponds (instead of using AMs, producers were said to use table salt, potassium permanganate and formalin), but higher in hatcheries. The most frequently used AB in East African countries appeared to be oxytetracycline. Farmers were described to follow a trial and error approach and look for advice for treatment in the internet. Even though disease and management practices were listed as constraints, respondents mentioned other priorities for the sector, including access to technology and management, sustainable market access and biodiversity issues between exotic and endemic species. Egypt and certain West African countries like Nigeria and Ghana were identified as countries where aquaculture is a larger and more developed sector with substantial disease problems that might drive the use of chemicals and AM.

Drivers of AMU and pathways of use

Figure 4A presents a general overview of the drivers for AMU mentioned by respondents throughout the discussions. These drivers help to think about the question of '*Where to intervene?*'. These drivers were grouped in biological, operational and governance, economic and behavioural drivers. Subsequently, information collated was illustrated as pathways to AMU (Figure 4B).

Firstly, biological factors were reported (1,2,3 in Figure 4A) as important causes leading to use of AM and chemicals, mainly in response to disease, due to environmental, host or pathogen causes. All the respondents mentioned water quality to be a crucial factor leading to stress and susceptibility of disease, and water as a vehicle of microorganisms and chemicals. Further, poor management practices (Factor 5) were described to be strongly interrelated, leading to stress and higher susceptibility to infection. Accordingly, in Egypt, poor water quality and management was reported to be a severe problem leading to susceptibility to disease and associated to the use of chemicals into the tilapia pond production. This occurs in a legislative and regulatory (Factor 14) context that prohibits the use of freshwater for culturing fish due to limited water resources, forcing farmers to use drainage water sources, containing pesticides and other chemicals that affect negatively the quality of the fish. Farmers are advised to invest in water treatment methods such as aeration, but uptake of these interventions and willingness to invest is unknown, as lack of capital and low profit margins were reported as constraints. Tilapia pond based production in Egypt, as other production systems in Vietnam in cages or ponds, were described to face constraints also due to the open nature of the system with poor biosecurity facilitating transmission of pathogens. While biological drivers (and their links with other factors) were deemed fundamental causes of AM and chemicals use in Asian countries and Egypt, respondents in Uganda, Kenya and Zambia unanimously attributed the lack of disease outbreaks and intensification of the sector as the reason for a current low AMU in the sector.

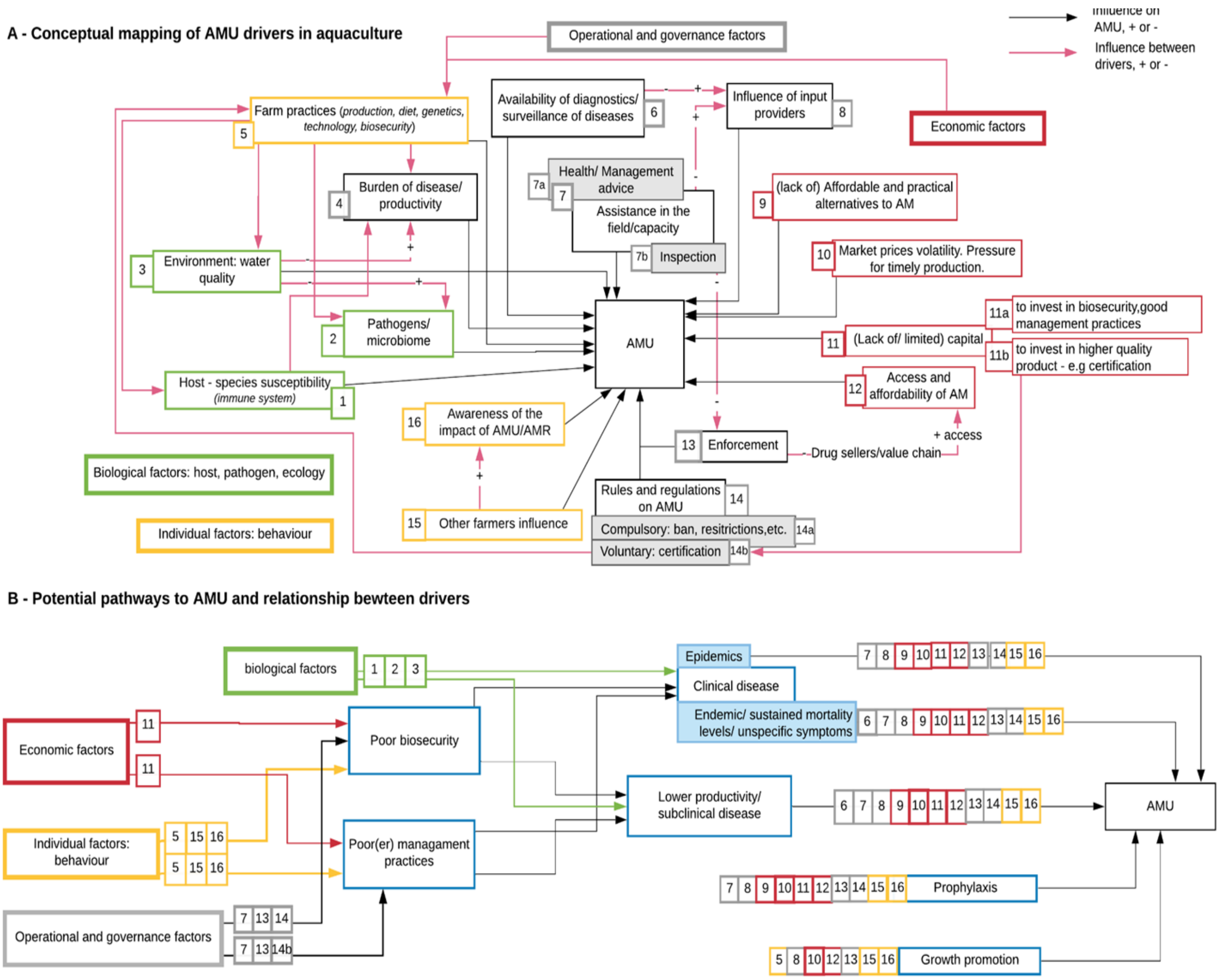

Figure 4 Drivers of AMU and pathways. **Section A** provides a general overview of main drivers of AMU in aquaculture systems in LMICs that influence use. In addition, potential links between drivers are shown. **Section B** outlines main pathways for AMU and points where different drivers have an influence.

Further, economic drivers were mentioned to be crucial. Commercial farmers were described to face pressure to deliver timely production in the light of price volatility. Therefore, production cannot be risked and AB are widely used in pangasius and shrimp production in Vietnam (*"respecting the withdrawal time, but in 100% use as prophylaxis"*). Incidence of disease was also mentioned as a driver (*"80% of commercial shrimp farms in Vietnam suffered white faeces disease last year and farmers were using AB as prophylaxis from the beginning to prevent it").* Other alternatives such as vaccines (Factor 9), were described to be impractical and not affordable even for commercial farmers in Vietnam, comparing the margin obtained using AB with the use of vaccines. Further, lack of capital and/or willingness to invest in biosecurity and good management was also described to drive AMU. Input providers mentioned that producers tried to invest in good management practices, but in the absence of significant better results in productivity and higher efforts, compared to their neighbour that only uses antibiotics, their interest to continue has dropped. In relation to this, in all the scenarios, producers were described to be highly influenced by what other producers do or use, particularly if it leads to higher yields (Factor 15). Private companies providing inputs were described to act as messengers of this information, witnessing this effect (Factor 8) and using it for their own products (such as feed additives and different compounds).

Regulatory frameworks and industry rules were described to influence use in different ways. Generally, implementation of the regulations appeared to be impeded by enforcement constraints. This was described to be associated to a lack of human and financial resources to conduct inspections at different points of the supply chain, or lack of stringent consequences to the breach of correct practices. Nevertheless, industry rules driving potential profit were described to influence positively management practices and prudent AMU in commercial systems, particularly for exporting commodities.

For each intervention type, the relevant drivers involved or targeted were identified (Table 3).

Table 3. Drivers of AMU related to the intervention types identified.

Action or intervention		Main drivers potentially involved or addressed
National strategies	National Action Plans, National Fish Health Management Strategy.	5 6 7 13 14 16
National Legislation and Regulatory framework: Act>Law>Regulation	*AM list of banned products; Dose (e.g. in feed), withdrawal periods*	13 14 12
	Prophylactic Health Products	13 14 8
	Role of veterinarian, licensing.	6 7 12 13 14
	Control of diseases	13 14 5
Market driven	Export requirements, demands from industry.	14
	Meta-governance arrangements – GSSI, ISEAL, AESAN GAP	
	Certification standards	5 8 11b 13 14b 15
	Enable exports markets	6 7 10 11 14
Technology and product solutions	Vaccines	1 2 6 7 9 11
	Feed additives, probiotics, prebiotics	1 2 6 7 8 9 15 1 5 9 11 15
Learning and raising awareness (behaviour)	Community engagement	15 16
	Media campaign	15 16
	Awareness campaign	16
	Training	5 16
On farm management	Best management practices, uptake of technology SPF seed. GIFT tilapia	1 2 3 5 7 11 15 16
	Environmental interventions	3 5 7 9 10 11 15 16
	Husbandry interventions	
Activities with co-benefits	Surveillance	6 7 14 15
	AMR/AMU	
	residues	
	Control of disease	
	Decision tools	7 16

Main drivers potentially involved: numbers correspond to Figure 4.

DISCUSSION

In this study, we developed a typology for interventions tackling AMU in aquaculture in LMICs. A total of seven distinct types of interventions were proposed based on seven variables. This typology is useful to understand how the problem of AMR is tackled in aquaculture, to identify similarities and differences across countries and to support evaluations of relevant interventions.

The typology developed is a multidimensional typology, as types are the result of the combination of different variables (or dimensions) that have clearly defined characteristics. It is a *conceptual* typology, previously described as *to explicate the meaning of a concept* (the interventions) *by mapping out its dimensions* (the variables) (Collier, LaPorte, and Seawright 2012). The typology was developed in an iterative process that included stages of reviews, conceptualisation, data collection, data analysis and interpretation. A critical step in this process was to conduct semi-structured interviews with aquaculture professionals to gather information on interventions, strategies, drivers and contexts. This information allowed elaborating the characteristics of the different types and identifying key drivers and consequently (further) potential intervention points in these aquaculture systems. To the authors' knowledge, this is the first typology of this kind for AMU interventions in the aquaculture sector in LMICs. Because it was developed based on available literature and semi-structured interviews with 17 professionals in the field, it may not be fully representative of all such interventions in this context. However, the typology can be applied, tested, expanded and refined in the AMU/AMR community as and when more data or information become available. For future work of this nature, it will be important to consider explicitly operational aspects, as these are often neglected and undervalued in the literature and may need to be obtained qualitatively in collaboration with designers and implementers.

When applying the typology, users can expect that each country shows a different profile of interventions based on the development of the sector and its characteristics, e.g. whether there are export and/or domestic activities, the proportion and stage of development of intensive commercial systems, and the diversity of species produced. Also, differences can be expected dependent on a countries AMU goals and its commitment to National Action Plans.

While the typology has been developed for the use of AMs, other important topics emerged. In particular the misuse of other chemicals such as malachite green or potassium permanganate ($KMnO_4$) and prophylactic medicinal products were of concern to the interviewees. It became evident that factors driving their use were similar to those described for AMs and that solutions may need to focus on underlying causes and structures. In any case, we suggest that a combination of interventions, or interventions combining different activities in the system will be necessary given the complexity of the problem and the multitude of drivers and pathways to AMR. Hence, a package of interventions may combine technical aspects (e.g. use of vaccines) with structural interventions, e.g. legislative and regulatory frameworks, effective enforcement systems, industry support, or changes in management practices.

An important use of the typology will be to characterise interventions to reduce AMU in aquaculture in LMICs in a standardised way as part of evaluation strategies. To date, the evidence on the impact of such interventions in aquaculture is scarce and scattered. This stands in stark contrast to the wide range of interventions proposed for public health and their respective evaluation plans. In aquaculture, positive effects of interventions are currently documented mainly for commercial systems that are driven by export activities. There is also some evidence being generated on the impact of small-scale interventions, such as ongoing randomised controlled trial probiotics project in India, Bangladesh and Kenya.

In order to conduct meaningful evaluations, it will be important to establish effective surveillance and monitoring systems for both AMU and AMR. To establish such systems and plan evaluations, it may be helpful to look at existing initiatives. For example, the JPIAMR funded project *Convergence in evaluation frameworks for integrated surveillance of antimicrobial use (AMU) and resistance (AMR)* is working on guidance for users interested in conducting evaluations of AMR and AMU surveillance taking an integrated perspective. The JPIAMR funded project *AMResilience* is an initiative that extends resilience and transformation frameworks for AMR previously developed at the global level, to assess national and regional one-health systems and interventions. As part of this project, a database on interventions is built, describing factors determining resilience and transformability. To date, up to 32 studies addressing surveillance systems of AMU and/or AMR in high income countries have been made available online (https://amr-resilience.gtglab.net/entries/). Notably, none of these studies addresses aquaculture systems. Around a third of these studies document or assess the effect of different interventions on AMR, such as the compulsory restrictions of AMU and voluntary withdrawal of AB in production of livestock; effect of surveillance programmes directly on AMR, or on other interventions as benchmarking; effect of prices of drugs, and also the effect of other interventions at post-harvest level or to treat effluents from hospitals with resistant bacteria. Previous studies like these may be helpful for people planning evaluations of interventions to reduce AMU in aquaculture systems in LMICs.

A lack of evaluation does not mean that there is no change or impact achieved. However, only with an evaluation, i.e. a systematic process to examine critically a project, programme or activity, it is possible to judge the effectiveness and value of an intervention. The interviews showed that many countries with important aquaculture production are in different stages of activities to tackle AMR in aquaculture influenced by the scale of production, awareness, and the perceived scale of the problem in a country, among other factors. In the future, countries may also wish to consider *AMR sensitive strategies* in line with recommendations made by the World Bank (2019). Our typology will help to characterise the different available and future interventions in a systematic way and thereby contribute to efforts that aim to study and promote solutions for the AMR challenge in aquaculture systems.

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APPENDIX 1 – **Interview guide**

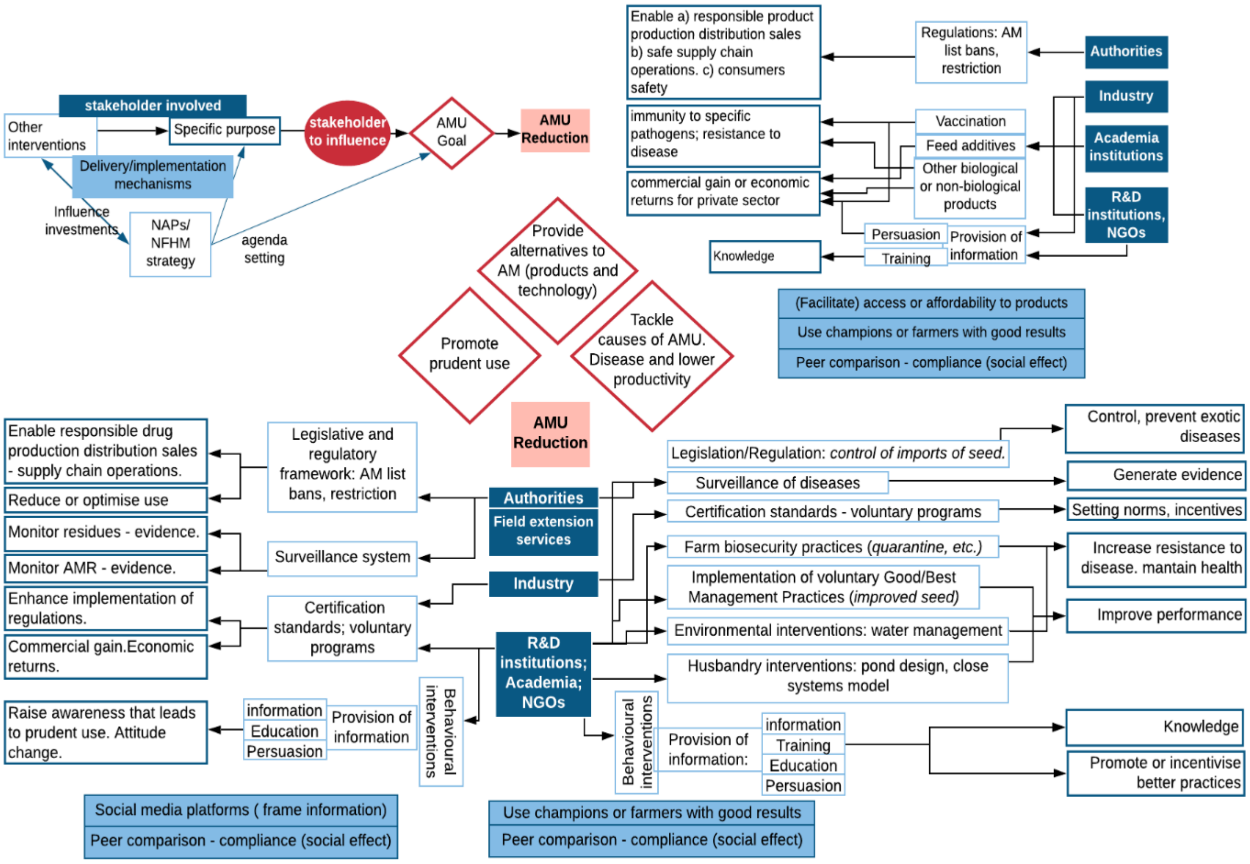
TYPOLOGY OF INTERVENTIONS AIMING TO REDUCE AMU IN AQUACULTURE SYSTEMS IN LOW AND MIDDLE INCOME COUNTRIES

A. Understand the background situation in the country in regards to AMR/AMU:
    - *What is the current AMU in aquaculture systems? What are the reasons for the use? (E.g. deficiencies in aquatic health management, intensification, to treat disease, as prophylaxis, etc.)*

B. Policies and interventions landscape in the country:
    - *What are the current antimicrobial resistance (AMR) policies in the country aiming to reduce directly or indirectly the use of AM in aquaculture? (E.g., legislation, national action plans, export requirements, certification programs, etc.)*
    - *Are incentives or disincentives being used to improve the acceptance of the policies or to reduce AMU? (Any strategy used that is creating incentives or disincentives regarding the use of AM).*
    - *Are there differences between aquatic and terrestrial policies for AMR?*
    - *Are there other soft policies or local initiatives driven by NGOs, local groups, cooperatives, academia, or between producers, to reduce the AMU? (awareness campaigns, information provision by key producers or ambassadors with useful advice,*

C. More specific information about the potential existing strategies to enquire for:
    a. *Production system.*
    b. *Type of strategy.*
    c. *Direct or indirectly aiming to reduce AMU – indirect would be any measure designed to address other aspect, but it has an effect on the use of AM.*
    d. *Stakeholder or decision maker to influence (producers, workers at the farm, dealers, industry, vets, agrovets, providers of health, etc.).*
    e. *Who is the designer of the strategy or intervention.*
    f. *Who is the implementer of the strategy of intervention.*
    g. *Timeline. What is the stage of the implementation.*
    h. *Compulsory or voluntary – what is the degree of obligation?*
    i. *What is the degree of enforcement and compliance? Challenges.*
    j. *Is the effect being measured and monitored? What is the perceived or measured effect?*
    k. *Is there any evaluation in place of the strategy?*

APPENDIX 2 - Overview and characterisation of interventions in aquaculture systems



Overview and characterisation of interventions in aquaculture systems