



AQUACULTURE DEVELOPMENT

8. Recommendations for prudent and responsible use of veterinary medicines in aquaculture



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PREPARATION OF THIS DOCUMENT

These guidelines are intended to provide general advice in support of the implementation of FAO's *Code of Conduct for Responsible Fisheries* (CCRF) (FAO, 1995) and thus have no formal legal status. The Code's Section 9 – Aquaculture Development directly addresses some of the broader issues related to the prudent and responsible use of veterinary medicines in aquaculture, including the need for appropriate environmental assessment and monitoring of drug and chemical use and impacts (Sections 9.1.5 and 9.2.5; the safe and appropriate use of feed additives (*inter alia*, including veterinary medicines added to feeds) (Section 9.4.3); the need to promote effective farm and fish health management practices, including the favouring of hygienic measures and vaccines and the safe, effective and minimal use of therapeutants, hormones and drugs, antibiotics and other disease-control chemicals (Section 9.4.4); the need for states to regulate the use of chemical inputs in aquaculture that are hazardous to human health and the environment (Section 9.4.5); and the need for states to ensure the safe disposal of veterinary medicines used in aquaculture (Section 9.4.6). The information presented in this document is meant to assist with consideration of issues related to the implementation of the provisions of the CCRF. Furthermore, any differences in the terminology employed should not be considered as a reinterpretation of the Code. These guidelines, which also support *The FAO Action Plan on Antimicrobial Resistance 2016–2020*, are intended to be flexible and capable of evolving as circumstances change or as new information becomes available.

These technical guidelines have been prepared under the coordination and technical supervision of Dr Melba B. Reantaso (Aquaculture Officer, Aquaculture Branch, FAO). Experts who contributed significantly to their preparation and finalization include: Drs J. Richard Arthur (Canada), Victoria Alday-Sanz and Carlos Zarza (Spain), Iddya Karunasagar (India), Mike Hine (New Zealand), David Huchzermeyer (South Africa), Peter Smith (Ireland), Snježana Zrnčić (Croatia), Kech Nicolas (France), Alessandro Patriarchi (World Health Organization) and Jeffrey Leujeune and Melba B. Reantaso (FAO).

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ABSTRACT

These Technical Guidelines on the Prudent and Responsible Use of Veterinary Medicines in Aquaculture (No. 5 Suppl. 8) are developed to support Section 9 – Aquaculture Development of FAO's *Code of Conduct for Responsible Fisheries (CCRF)* and *The FAO Action Plan on Antimicrobial Resistance 2016–2020*. They also support the international aquatic animal health standards of the World Organisation for Animal Health (OIE), the food safety standards of the FAO/World Health Organization (WHO) Codex Alimentarius and the One Health platform under the FAO/OIE/WHO Tripartite Collaboration on antimicrobial resistance (AMR). Their objective is to assist countries in encouraging the prudent and responsible use of veterinary medicines (antimicrobial agents and other chemotherapeutants) in aquaculture production through appropriate government regulation and the promotion and encouragement of awareness and responsible use by the private sector. They emphasize, among the guiding principles, that responsible use of veterinary medicines in aquaculture requires collaboration among all stakeholders and a strong commitment to governance, awareness, best practices, surveillance and research, including monitoring of AMR, tracking of antimicrobial usage (AMU), assessing risk in different settings and evaluating strategies to reduce AMR and maintain efficacy of antimicrobial agents. They provide general guidance on the use of veterinary medicines in aquaculture to responsible government agencies, private-sector aquaculture producers and aquatic animal health professionals.

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ACRONYMS AND ABBREVIATIONS

AGAH	Animal Health Service (of the FAO)
AGFF	Food Safety and Quality (of the FAO)
AMR	Antimicrobial resistance
AMU	Antimicrobial use
BMPs	Better management practices
CCRF	Code of Conduct for Responsible Fisheries (of the FAO)
CIDA	Canadian International Development Agency
CoCs	Codes of conduct
COFI	Committee on Fisheries (of the FAO)
FAO	Food and Agriculture Organization of the United Nations
FCR	Feed conversion ratio
FI	Fisheries and Aquaculture Department (of the FAO)
GAqPs	Good aquaculture practices
HAEI	Human-animal-ecosystem interface
HH	High health
IACG	Interagency Coordination Group
IAEA	International Atomic Energy Agency
ICES	International Council for the Exploration of the Sea
IMO	International Maritime Organization
LIFDCs	Low Income Food Deficit Countries
MPTF	Multi-partner trust fund
MRLs	Maximum residue limits
NAP	National action plan
NGOs	Non-governmental organizations
NSAAH	National strategy on aquatic animal health
OIE	World Organisation for Animal Health (formerly the Office International des Épipizooties)

PMP	Progressive Management Pathway
PMP/AB	Progressive Management Pathway for Improving Aquaculture Biosecurity
SEAFDEC	Southeast Asian Fisheries Development Center
SOPs	Standard operating procedures
SPF	Specific pathogen free
SPR	Specific pathogen resistant
TAADs	Transboundary aquatic animal diseases
UN	United Nations
UNCED	United Nations Conference on Environment and Development
UNESCO-IOC	Intergovernmental Oceanographic Commission of the United Nations Educational, Scientific and Cultural Organization
UNEP	United Nations Environment Programme
UNGA	United Nations General Assembly
USFDA	United States Food and Drug Administration
UV	Ultraviolet
WHO	World Health Organization
WMO	World Meteorological Organization

BACKGROUND

1. From ancient times, fishing from oceans, lakes and rivers has been a major source of food, a provider of employment and other economic benefits for humanity. Ocean productivity seemed particularly unlimited. However, with increased knowledge and the dynamic development of fisheries and aquaculture, it was realized that living aquatic resources, although renewable, are not infinite and need to be properly managed, if their contribution to the nutritional, economic and social well-being of the growing world's population was to be sustained.

2. However, for nearly three decades, because of the dramatic increase of pollution, abusive fishing techniques worldwide, and illegal, unreported and unregulated fishing, catches and landings have been shrinking and fish stocks declining, often at alarming rates.

3. Stock depletion has negative implications for food security and economic development and reduces social welfare in countries around the world, especially those relying on fish as their main source of animal protein and income such as subsistence fishers in developing countries. Living aquatic resources need to be properly managed, if their benefits to society are to be sustainable.

4. Sustainability of societal benefits requires a recovery of depleted stocks and maintenance of the still-healthy ones, through sound management. In this regard, the adoption of the United Nations Convention on the Law of the Sea, in 1982 was instrumental. The law provides a new framework for the better management of marine resources. The new legal regime of the oceans gave coastal States rights and responsibilities for the management and use of fishery resources within the areas of their national jurisdiction, which embrace some 90 percent of the world's marine fisheries.

5. In recent years, world fisheries have become dynamically developing sectors of the food industry, and many States have striven to take advantage of their new opportunities by investing in modern fishing fleets and processing factories in response to growing international demand for fish and fishery products. It became clear,

however, that many fisheries resources could not sustain an often uncontrolled increase of exploitation. Overexploitation of important fish stocks, modifications of ecosystems, significant economic losses, and international conflicts on management and fish trade still threaten the long-term sustainability of fisheries and the contribution of fisheries to food supply.

6. In light of this situation, while recognizing that the recovery of depleted stocks is still urgent and avoiding depleting still-healthy stocks as important, FAO Member States have expressed the need to further develop aquaculture as the only immediate way to bridge the gap between the dipping capture fisheries output and the increasing world demand for seafood.

7. Indeed, in the last three decades, aquaculture has recorded a significant and most rapid growth among the food-producing sectors and has developed into a globally robust and vital industry. However, aquaculture also has been shown at times to carry the potential to cause significant environmentally and socially adverse impacts.

8. Thus, the Nineteenth Session of the FAO Committee on Fisheries (COFI), held in March 1991, recommended that new approaches to fisheries and aquaculture management embracing conservation and environmental, as well as social and economic, considerations were urgently needed. FAO was asked to develop the concept of responsible fisheries and elaborate a Code of Conduct to foster its application.

9. Subsequently, the Government of Mexico, in collaboration with FAO, organized an International Conference on Responsible Fishing in Cancún in May 1992. The Declaration of Cancún, endorsed at that Conference, was brought to the attention of the United Nations Conference on Environment and Development Summit in Rio de Janeiro, Brazil, in June 1992, which supported the preparation of a Code of Conduct for Responsible Fisheries. The FAO Technical

Consultation on High Seas Fishing, held in September 1992, further recommended the elaboration of a code to address the issues regarding high seas fisheries.

10. The One Hundred and Second Session of the FAO Council, held in November 1992, discussed the elaboration of the Code, recommending that priority be given to high seas issues and requested that proposals for the Code be presented to the 1993 session of the Committee on Fisheries.

11. The twentieth session of COFI, held in March 1993, examined in general the proposed framework and content for such a Code, including the elaboration of guidelines, and endorsed a time frame for the further elaboration of the Code. It also requested FAO to prepare, on a “fast track” basis, as part of the Code, proposals to prevent reflagging of fishing vessels which affect conservation and management measures on the high seas. This resulted in the FAO Conference, at its Twenty-seventh Session in November 1993, adopting the Agreement to Promote Compliance with International Conservation and Management Measures by Fishing Vessels on the High Seas, which, according to FAO Conference Resolution 15/93, forms an integral part of the Code. It was also recognized and confirmed that issues of responsible aquaculture development and aquaculture sustainability should be addressed in the formulation process so that these be appropriately covered in the envisaged Code.

12. This implicit recognition of the importance of governance in aquaculture is underlined in Article 9.1.1 of the Code, which requires states to “establish, maintain and develop an appropriate legal and administrative framework to facilitate the development of responsible aquaculture”. In addition, at the beginning of the new millennium, there is growing recognition of the significant potential for the use of ocean and coastal waters for mariculture expansion. The outstanding issue in this area is that, unlike in capture fisheries, the existing applicable principles of public international law and treaty provisions provide little guidance on the conduct of aquaculture operations in these waters. Yet, experts agree that most of the future aquaculture expansion will occur in the seas and oceans, certainly further offshore, perhaps even

as far as the high seas. The regulatory vacuum for aquaculture in the high seas would have to be addressed should aquaculture operations expand there.

13. The Code was formulated so as to be interpreted and applied in conformity with the relevant rules of international law, as reflected in the 10 December 1982 United Nations Convention on the Law of the Sea. The Code is also in line with the Agreement for the Implementation of the Provisions of this Law, namely the 1995 Conservation and Management of Straddling Fish Stocks and Highly Migratory Fish Stocks. It is equally in line with, inter alia, the 1992 Declaration of Cancún and the 1992 Rio Declaration on Environment and Development, in particular Chapter 17 of Agenda 21.

14. The development of the Code was carried out by FAO in consultation and collaboration with relevant United Nations Agencies and other international organizations, including non-governmental organizations.

15. The Code of Conduct consists of five introductory articles: Nature and scope; Objectives; Relationship with other international instruments; Implementation, monitoring and updating; and Special requirements of developing countries. These introductory articles are followed by an article on General principles, which precedes the six thematic articles on Fisheries management, Fishing operations, Aquaculture development, Integration of fisheries into coastal area management, Post-harvest practices and trade, and Fisheries research. As already mentioned, the Agreement to Promote Compliance with International Conservation and Management Measures by Fishing Vessels on the High Seas forms an integral part of the Code.

16. The Code is voluntary. However, certain parts of it are based on relevant rules of international law, as reflected in the United Nations Convention on the Law of the Sea of 10 December 1982. In capture fisheries, the Code also contains provisions that may be or have already been given binding effect by means of other obligatory legal instruments amongst the Parties, such as the Agreement to Promote Compliance with Conservation and Management Measures by Fishing Vessels on the High Seas, 1993. In aquaculture, the provisions of

the Code implicitly encourage participatory governance of the sector, which extends from industry self-regulation, to co-management of the sector by industry representatives and government regulators and to community partnerships. Compliance is self or enforced by peer pressure, with industry organizations having the ability to exclude those who do not comply and governments only checking periodically.

17. The Twenty-eighth Session of the Conference in Resolution 4/95 adopted the Code of Conduct for Responsible Fisheries on 31 October 1995. The same Resolution requested FAO inter alia to elaborate appropriate technical guidelines in support of the implementation of the Code in collaboration with members and interested relevant organizations.

18. The expanding role and increasing contribution of aquaculture to economic growth, social welfare as well as global food security was recognized and reiterated at international levels such as the 1995 FAO/ Japan Conference on the Contribution of Fisheries and Aquaculture to Food Security, the 1996 World Food Summit, the 1999 Ministerial Meeting on Fisheries, the 2000 FAO/NACA [Network of Aquaculture Centres in Asia and the Pacific] Conference on Aquaculture in the Third Millennium and its Bangkok Declaration and Strategy, and most recently, the 2009 World Summit on Food Security.

19. The application of the ecosystem approach to fisheries and aquaculture as strategies for the development of the sector contributes to the implementation of the provisions of the Code, thereby enforcing the technical, ecological, economic and social sustainability of the industry.

1. INTRODUCTION

Aquaculture continues to be the world's fastest-growing food production sector and the farming, trading, and processing of aquaculture products continue to be of major social and economic importance. Aquaculture enjoyed high annual growth rates in the 1980s and 1990s of 11.3 and 9.95 percent, respectively, excluding aquatic plants (FAO, 2019a). Although annual growth rates declined afterwards, aquaculture, excluding aquatic plants, still grew at an average annual growth rate of 5.47 percent during the period 2000-2017 with double digit growth still occurring in a small number of countries, particularly in Africa from 2006 to 2010 (FAO, 2018b, FAO, 2019a). In 2017, aquaculture (excluding aquatic plants) represented 46 percent of the total global supply of aquatic animals destined for human consumption. Asia produces 89 percent of the current global production with China, being by far the major producer of farmed food fish, producing 58 percent of total global aquaculture production, excluding aquatic plants (FAO, 2019a).

Aquaculture is thus expected to play a key role in meeting the increasing worldwide demands for aquatic animal production. By 2030, aquaculture is predicted to make up 62 percent of foodfish production and is expected to become the dominant force in world foodfish supply (World Bank, 2013). Achieving the sustainable development of global aquaculture is, therefore, an imperative agenda for the global economy.

Aquaculture also has the potential to provide increased livelihood opportunities and economic security, particularly in developing and Low Income Food Deficit Countries (LIFDCs), where it is widely perceived as an important weapon in the global fight against malnutrition and poverty. To achieve this potential, aquaculture will need to provide both a wide range of high-value products for international markets and an abundant supply of low-cost, staple foods for domestic consumption.

Diseases are a primary constraint to the culture of many aquatic species. Although the capability to manage aquaculture health issues has increased tremendously in the last 30 years, the rapid development of the aquaculture sector continues to generate new challenges. This is particularly apparent with increased interest in species diversification, increased stocking densities and new grow-out techniques. In addition to the obvious effects of large-scale aquaculture losses on rural communities, diseases (particularly those causing mass mortalities) cause considerable impacts on investor confidence.

The increasing intensification and diversification of global aquaculture has led to the dramatic growth of the sector and a corresponding increase in its importance as a source of protein for a growing human population, creator of jobs and an important source of foreign export earnings for many developed and developing countries. However, as is the case in commercial livestock and poultry production, the expansion of commercial aquaculture has necessitated the routine use of veterinary medicines to prevent and treat disease outbreaks due to pathogens, assure healthy stocks and maximize production and welfare of the farmed animals. While the globalization of the aquaculture sector has created many new market opportunities for farmed aquatic animals, it has simultaneously facilitated the spread of their pathogens and diseases. Currently, there exists the general perception, worldwide, that veterinary medicines (and antimicrobial agents in particular) have been imprudently used in aquaculture. The misuse of veterinary medicines by the aquaculture sector also has potential negative implications for the environment and human food safety, may lead to the development of resistance to antimicrobial agents useful in human medicine, and has the potential to impact free trade. There is also concern regarding the lack of approved veterinary medicines for certain aquaculture species and diseases. The concern is likely higher when regulatory processes for aquatic veterinary medicines are not well developed. Significant variation in regulatory frameworks and enforcement in different countries has the potential to seriously impede the continued growth of the aquaculture sector.

These perceptions often cast aquaculture in a negative light and have implications for the continued expansion of the sector and its role in addressing the growing need for fish and shellfish for an expanding global population. While government has a key role to play in promoting the sustainability of aquaculture production and protecting public health, ensuring the judicious use of veterinary medicines does not rest with government alone. It is a shared responsibility of all involved in the sector, including aquaculture producers, aquatic animal health professionals, feed, drug and chemical manufacturers and sales persons, and the general public.

FAO encourages Member Countries to develop and formalize national strategies on aquatic animal health (NSAAH) and health management procedures (FAO, 2007). The prudent and responsible use of veterinary medicines is an essential component and element of a NSAAH – a broad yet comprehensive strategy to build and enhance capacity for the management of national aquatic biosecurity and aquatic animal health (see, for example, Government of Bosnia and Herzegovina, State Veterinary Office, 2009; MFFAM, 2016). The NSAAH contains the national action plans (NAPs) at the short-, medium- and long-term using phased implementation based on national needs and priorities; outlines the programmes and projects that will assist in developing a national approach to overall management of aquatic animal health; and includes an implementation plan that identifies the activities that must be accomplished by government, academia and the private sector. FAO also recommends to use the Progressive Management Pathway (PMP), an extension of the Progressive Control Pathway, a step-wise risk management pathway used to develop and monitor national strategies for important livestock diseases such as foot-and-mouth disease, African animal trypanosomiasis, peste des petits ruminants and rabies. The PMP for improving aquaculture biosecurity (PMP/AB) has four stages, follows the principles of being risk-based, progressive and collaborative and should adhere to international standards (e.g. OIE) and regional agreements (both obligatory and voluntary), including countries sharing transboundary waterways. Responsibilities must be shared among key national, regional and international stakeholders from government, the production sector and academia as well as other players in the value

chain, building on each other's strengths towards a common goal (Bondad-Reantaso *et al.*, 2018; FAO, 2018b, 2019b). The NSAAH is a basic element and a necessary step of Stage 1 of the PMP/AB.

Access to safe and effective veterinary medicines or drugs is essential to the success of semi-intensive and intensive aquaculture, as in some instances entire stocks may be lost if such drugs are not available. However, if inappropriately used, such drugs may be ineffective or may lead to unacceptable residue levels in aquaculture products. The presence of residues in exported aquaculture products that are above the importing country's acceptable levels may lead to bans on importation, import rejections and detentions, with severe impacts on a country's aquaculture industry. It is thus essential that countries establish mechanisms (e.g. laws, regulations, guidelines, standard operating procedures (SOPs), better management practices (BMPs)) to ensure the safe use of veterinary drugs, along with testing and monitoring programmes, to assure trading partners that national aquaculture products are safe and meet importing-country standards. Safe and effective veterinary medicines need to be available for efficient aquaculture production, and their use should be in line with established principles on prudent use of veterinary medicines to safeguard public and animal health. The use of such medicines should be part of national and on-farm biosecurity plans and in accordance with an overall national policy for aquaculture.

1.1 Statement of purpose

These Technical Guidelines on Prudent and Responsible Use of Veterinary Medicines in Aquaculture are developed to support sections of the Code addressing responsible fisheries management (Article 7), aquaculture development (Article 9), international trade (Article 11) and fisheries research (Article 12). Their objective is to assist countries in encouraging the prudent and responsible use of veterinary medicines in aquaculture production through appropriate government regulation and the promotion and encouragement of awareness and responsible use by the private sector.

1.2 Structure and content of this document

This document is the eighth in the series *FAO Technical Guidelines for Responsible Fisheries* (see, for example FAO, 1997, 2007) and is thus structured similarly to previously published issues of this series. The Technical Guidelines present eight Guiding Principles – “doing the right thing” – in all circumstances, irrespective of changes in the goals, strategies, work plan, structure or management of, e.g. an NSAAH or an Aquaculture Development Plan. The Guiding Principles accept and incorporate relevant international aquatic animal health standards (i.e. the *OIE Aquatic Animal Health Code, 2018* (OIE, 2018a)) and other relevant regional agreements to ensure harmonization, transparency and equivalence and that the country be internationally recognized with respect to national aquatic animal health status.

The Guiding Principles were based on, for example, the *FAO Technical Guidelines on Health Management for Responsible Movement of Live Aquatic Animals* (FAO, 2007) as well as some general principles concerning economic, social and environmental conduct.

1.3 Guiding Principles

The following Guiding Principles form the basis for this document:

- States should:
 - establish and maintain an appropriate legal and administrative framework which facilitates the development of responsible aquaculture;
 - promote effective farm husbandry and aquatic animal management practices favouring the use of preventative hygienic measures and vaccines to limit exposure to and impacts of pathogens and disease. Such measures include, for example, the development and use of NSAAH; biosecurity plans and policies for sustainable aquaculture; Code of Conduct; BMPs/good aquaculture practices (BMPs/

- GAQPs); health certification; specific pathogen free (SPF), specific pathogen resistant (SPR) and high health (HH) stocks; and quarantine and vaccination protocols;
- regulate the use of chemical inputs in aquaculture that represent a risk to human health and the environment; safe, effective and minimal use of veterinary medicines should be ensured;
 - require that the disposal of wastes such as offal, sludge, dead or diseased fish, excess veterinary drugs and other hazardous chemical inputs does not constitute a hazard to human health or the environment;
 - establish effective procedures specific to aquaculture to undertake appropriate environmental assessment and monitoring with the aim of minimizing adverse ecological changes and related economic and social consequences resulting from the use of veterinary medicines and other aquaculture activities;
 - have mechanisms in place to ensure that authorized veterinary drugs are used properly in accordance with label indications. Mechanisms that should be considered include the implementation of appropriately designed monitoring programmes for the effectiveness of diagnostics and therapy, presence of residues in food and occurrence of antimicrobial resistance (AMR);
 - strengthen ability of aquatic animal health specialists to collect necessary epidemiological data in the field;
 - ensure that laboratories used for testing use only appropriately validated diagnostic methods that are “fit for purpose”;
 - increase the use of risk analysis methodologies to understand and reduce the risk associated with the use of veterinary medicines in aquaculture. Foodborne AMR analysis in aquaculture should give consideration, as appropriate, to relevant international documents (for example, the WHO’s *Guidelines for Risk Analysis for Foodborne Antimicrobial Resistance* (WHO, 2011), and *Global Action Plan on Antimicrobial Resistance* (WHO, 2015); Chapter 6.5 of the OIE’s *Aquatic Animal Health Code* (OIE, 2018a) and

- recommendations of the *FAO/WHO/OIE Expert Meeting on Critically Important Antimicrobials* (FAO, 2008)) for setting priorities for risk assessment and/or risk management activities); and
- develop and formalize NSAAH and health management procedures that incorporate mechanisms for the prudent and responsible use of veterinary medicines. Such strategies and procedures should adhere to international standards (i.e. OIE Aquatic Code Chapter 6.4; Codex Guidelines for risk analysis of foodborne antimicrobial resistance (CAC, 2011)) and other regional agreements (where they exist) and be harmonized on as wide a basis as possible.
- Safe and effective veterinary medicines are essential to efficient commercial aquaculture production, and their use should be in line with established principles on their prudent use to safeguard public and animal health.
 - The use of veterinary medicines should be subject to the oversight of aquatic animal health professionals qualified by training and experience as recognized by national or regional regulatory authorities.
 - The appropriate use of antimicrobial agents and other veterinary medicines in aquaculture production is a clinical decision that should be made based on experience and local expertise of the prescribing aquatic animal health professional and an accurate diagnosis based on appropriate diagnostic procedures. Judicious use of veterinary medicines in aquaculture production should be the normal practice.
 - Responsible use of veterinary medicines in aquaculture requires a strong commitment to governance, awareness, best practices, surveillance and research, including monitoring of AMR, tracking of antimicrobial usage (AMU), assessing risk in different settings and evaluating strategies to reduce AMR and maintain efficacy of antimicrobial agents.
 - Collaboration among all stakeholders including state and non-state actors, primary producers, public institutions, aquatic veterinarians and aquatic animal health specialists and

scientists, and the general public is important to achieve prudent and responsible use of veterinary medicines in aquaculture production.

- Developed countries should assist developing-country trading partners to meet national and international standards with regard to the responsible use of veterinary medicines in aquaculture to minimize potential impacts on the environment, human health and domestic and international trade.
- Individual countries may need to adapt, modify or vary these Technical Guidelines to suit their respective situations and resources, while maintaining the spirit of these principles.

1.4 Definitions

Antibiograms – An overall profile of antimicrobial susceptibility testing results of a specific microorganism to disc diffusion susceptibility testing.

Antibiotics – Drugs of natural or synthetic origin, with the capacity to inhibit the growth of or to kill bacteria. Antibiotics that are sufficiently non-toxic to the host are used as chemotherapeutic agents in the treatment of infectious diseases of man, animals and plants (FAO, 2005).

Antimicrobial agents – Any substances of natural, semisynthetic or synthetic origin that at *in vivo* concentrations kill or inhibit the growth of microorganisms by interacting with a specific target (FAO/WHO Codex Alimentarius, 2015).

Aquatic animals – All life stages (including eggs and gametes) of fish, molluscs, crustaceans and amphibians originating from aquaculture establishments or removed from the wild, for farming purposes, for release into the aquatic environment, for human consumption or for ornamental purposes (modified from OIE, 2018b).

Aquatic animal health management – The sum of all actions taken by government, academia and private sector to prevent losses in cultured or wild populations of aquatic animals due to disease, and to ensure the optimal growth and health of the cultured stocks.

Aquatic animal health professionals – Veterinarians working in the field of aquatic animal health and non-veterinary aquatic animal health specialists trained and authorized to prescribe and/or supervise the use of veterinary medicines in aquaculture production facilities.

Aquatic animal health specialists – Scientists, veterinarians and other experts with specialized training and expertise in one or more areas related to aquatic animal health (e.g. aquaculture health management, aquatic epidemiology, disease diagnosis, molecular biology, biosecurity, risk analysis).

Bacteria – Unicellular prokaryotic microorganisms that multiply by cell division, typically have a cell wall and may be aerobic or anaerobic, motile or non-motile, free-living, saprophytic or pathogenic (modified from FAO, 2001).

Biosecurity – The sum total of the activities and measures taken by a region, country, group of aquaculture producers or single aquaculture production facility to protect its natural aquatic resources, capture fisheries, aquaculture, biodiversity and/or cultured stocks and the people who depend on them from the possible negative impacts resulting from the introduction and spread of serious aquatic animal diseases (modified from FAO, 2007).

Chemotherapeutants – Chemicals used to treat infections or non-infectious disorders (modified from FAO, 2001).

Competent Authority – The Veterinary Services, or other authority of an OIE Member Country, e.g. Fisheries and Aquaculture Authority, having the responsibility and competence for ensuring or supervising the implementation of the aquatic animal health measures or other standards in the OIE *Aquatic Animal Health Code* (modified from OIE, 2018a).

Diseases – Clinical or non-clinical infections with one or more pathogenic agents (OIE, 2018b).

Disinfectants – Chemical compounds capable of destroying microorganisms or inhibiting their growth or survival ability (modified from OIE, 2018b).

Extralabel/offlabel use – The use of an antimicrobial agent that is not in accordance with the approved product labelling. Such uses may be allowed under certain national regulations (FAO/WHO Codex Alimentarius, 2015).

Feed conversion ratio (FCR) – A measure of aquaculture production efficiency, expressed as a comparison of the amount of feed used per unit weight gain of the species being grown (modified from Hasan and Soto, 2017).

High health (HH) – Aquatic animals originating from a production facility having specific pathogen free (SPF) status, but which are now held in commercial facilities under less rigorous biosecurity conditions and thus a lower guarantee of health status. Once animals leave a HH production facility, they are no longer considered to have high health status (FAO, 2007).

Inter-laboratory comparison (ring test) – Any evaluation of assay performance and/or laboratory competence in the testing of defined samples by two or more laboratories; one laboratory may act as the reference in defining test sample attributes (OIE, 2018a).

Maximum residue limit (MRL) – The maximum allowed concentration of residue in a food product obtained from an animal that has received a veterinary medicine or that has been exposed to a biocidal product for use in animal husbandry.

Microorganisms – Principally viruses, bacteria and fungi (microscopic species, and taxonomically related macroscopic species). Microscopic protists (Protozoa) and algae may also be referred to as microorganisms (FAO, 2001).

Monitoring – The intermittent performance and analysis of routine measurements and observations, aimed at detecting changes in the environment or health status of a population (OIE, 2018a).

Pathogens – Infectious agents capable of causing disease (FAO, 2007).

Quarantine – Maintaining a group of aquatic animals and the water in which they live in isolation with no direct or indirect contact with other aquatic animals, in order to undergo observation for a specified length of time and, if appropriate, testing and treatment, including proper treatment of the effluent waters (OIE, 2018b).

Risk – The likelihood of the occurrence and the likely magnitude of the biological and economic consequences of an adverse event or effect to animal or human health (OIE, 2018b).

Specific pathogen free (SPF) – Aquatic animals that have been produced and are tested and held under rigorous conditions of biosecurity that provide assurances that they are free of certain specified pathogens. Once animals leave a SPF facility, they are no longer considered to have SPF status (FAO, 2007).

Specific pathogen resistant (SPR) – A stock of aquatic animals that has been bred to have genetic resistance to or improved tolerance of infection by a specific pathogen (FAO, 2007).

Surveillance – A systematic series of investigations of a given population of aquatic animals to detect the occurrence of disease for control purposes, and which may involve testing samples of a population (OIE, 2018b).

Transboundary aquatic animal diseases (TAADs) – Aquatic animal diseases that are highly contagious or transmissible, with the potential for very rapid spread irrespective of national borders that cause serious socio-economic and possibly public health consequences (FAO, 2007).

Vaccines – Antigen preparations derived from whole or extracted parts of infectious organisms, which are used to enhance the specific immune response of a susceptible host (modified from FAO, 2001).

Veterinary medicines – Any substance or combination of substances presented for treating or preventing disease in animals or which may be administered to animals to restore health, and correct or modify physiological functions in animals (modified from EU, 2004).

Viruses – One of a group of minute infectious agents, characterized by a lack of independent metabolism and by the ability to replicate only within living host cells (FAO, 2001).

2. APPLICATION OF THE CCRF TO THE USE OF VETERINARY MEDICINES IN AQUACULTURE

The CCRF (FAO, 1995) directly addresses the need to promote the prudent and responsible use of veterinary medicines in the production of farmed aquatic animals. The relevant sections of the Code are listed below.

2.1 Article 9 – Aquaculture development

The need for states to promote and ensure the prudent and responsible use of veterinary medicines in aquaculture is explicitly stated in Article 9 of the Code, which deals with the responsible development of aquaculture, and, in particular, in Sections 9.1, 9.2 and 9.4 and their subsections. These include: (Section 9.1.1) the need to establish, maintain and develop an appropriate legal and administrative framework; (Sections 9.1.5 and 9.2.5) the need for appropriate environmental assessment and monitoring of the use and impacts of drugs and chemicals; (Sections 9.1.5 and 9.4.3) the need for the safe and appropriate use of feed additives (including, *inter alia*, the use of veterinary medicines added to feeds); (Section 9.4.4) the need to promote effective farm and fish health management practices, including the favouring of hygienic measures and vaccines and the safe, effective and minimal use of therapeutants, hormones and drugs, antibiotics and other disease control chemicals; (Section 9.4.5) the need for states to regulate the use of chemical inputs in aquaculture that are hazardous to human health and the environment; and (Section 9.4.6) the need for states to ensure the safe disposal of veterinary medicines used in aquaculture. The relevant portions of these sections are given below:

9.1 Responsible development of aquaculture, including culture-based fisheries, in areas under national jurisdiction

9.1.1 States should establish, maintain and develop an appropriate legal and administrative framework which facilitates the development of responsible aquaculture.

9.1.5 States should establish effective procedures specific to aquaculture to undertake appropriate environmental assessment and monitoring with the aim of minimizing adverse ecological changes and related economic and social consequences resulting from water extraction, land use, discharge of effluents, use of drugs and chemicals, and other aquaculture activities.

9.2 Responsible development of aquaculture including culture-based fisheries within transboundary ecosystems

9.2.5 States should cooperate in the development of appropriate mechanisms, when required, to monitor the impacts of inputs used in aquaculture.

9.4 Responsible aquaculture at the production level

9.4.3 States should promote efforts which improve selection and use of appropriate feeds, feed additives and fertilizers, including manures.

9.4.4 States should promote effective farm and fish health management practices favouring hygienic measures and vaccines. Safe, effective and minimal use of therapeutants, hormones and drugs, antibiotics and other disease control chemicals should be ensured.

9.4.5 States should regulate the use of chemical inputs in aquaculture which are hazardous to human health and the environment.

9.4.6 States should require that the disposal of wastes such as offal, sludge, dead or diseased fish, excess veterinary drugs and other hazardous chemical inputs does not constitute a hazard to human health and the environment.

3. TOWARDS RESPONSIBLE USE OF VETERINARY MEDICINES IN AQUACULTURE

3.1 International setting

Some of the earliest publications related to surveys and the prudent and responsible use of veterinary medicines in aquaculture include:

- a survey by Primavera *et al.* (1993) of the chemicals and biological products used in intensive shrimp farming in the Philippines;
- a report by the International Council for the Exploration of the Sea (ICES) (1994) on the chemicals used in aquaculture;
- the proceeding of the meeting organized by FAO, the Canadian International Development Agency (CIDA) and the Southeast Asian Fisheries Development Center (SEAFDEC) on the use of chemicals in aquaculture in Asia, held in Tigbauan, Philippines in 1996 (see Arthur, Lavilla-Pitogo and Subasinghe, 2000);
- the report by the International Maritime Organization (IMO)/FAO/the Intergovernmental Oceanographic Commission of the United Nations Educational, Scientific and Cultural Organization (UNESCO-IOC)/the World Meteorological Organization (WMO)/WHO/the International Atomic Energy Agency (IAEA)/the United Nations (UN)/the United Nations Environment Programme (UNEP) Joint Group of Experts on the Scientific Aspects of Marine Environmental Protection (GESAMP, 1997) entitled “Towards safe and effective use of chemicals in coastal aquaculture”; and
- the publication of Gräslund, Holmström and Wahlström (2003) on the results of a field survey of chemicals and biological products used in shrimp farming.

Other milestones include the Joint FAO/WHO/OIE Expert Consultation on Antimicrobial Use in Aquaculture and Antimicrobial Resistance, held in Seoul, South Korea in 2006 (see WHO/FAO/OIE, 2006), and a global survey conducted by FAO in 2009 that involved sending questionnaires to global contacts by e-mail, the organizing of in-country workshops

attended by industry stakeholders (farmers, feed millers, drug suppliers, retailers, etc.), and visits to stores, farms and feed mills (see Bondad-Reantaso, Arthur and Subasinghe, 2012).

The international situation regarding aquaculture and the use of veterinary medicines has changed dramatically during the past few decades. The globalization of trade in aquatic animal products and the rise in prominence of aquaculture as a primary supplier of the world's aquatic food supply has been associated with the culture of new aquatic species, the movement of aquatic organisms to new countries and continents (often accompanied by their pathogens) and a general trend towards intensification of production methods and the industrialization of the sector. These trends have all led towards increased reliance on veterinary medicines to ensure successful production. A number of veterinary medicines used in aquaculture have been shown to have potential harmful effects on human health (e.g. chloramphenicol, malachite green, gentian violet, nitrofurans, fluoroquinolones and quinolones), leading to bans on their use in aquaculture, reducing the limited arsenal of drugs that are available for disease treatment. At the same time, global efforts to contain development of AMR have intensified, and guidelines for the prudent use of antimicrobial agents have been introduced and developed by several organizations (see, for example, Teale and Moulin, 2012).

Improved technology has significantly increased the capacity to detect trace amounts of residue of banned or restricted substances, leading to ever-decreasing detection levels. Consumer awareness and concern over the possible health and environmental hazards posed by the use and misuse of veterinary medicines in aquaculture has also grown. The result of these trends has been more stringent testing and inspection standards by importing countries and difficulties in some developing countries meeting importing country requirements (leading to occasional product bans and, due to lack of capacity, to some developing countries having different standards for aquaculture products directed to export and domestic markets).

In general, the global trend is toward more stringent and uniform standards and a more prudent and responsible use of veterinary medicines by the aquaculture sector. The maturation of some aquaculture sectors, such as the salmon industry in Norway and yellowtail culture in Japan has shown the great potential that preventative methods (vaccines and improved husbandry) and strong legislative controls have towards reducing the aquaculture sector's reliance on veterinary medicines to achieve improved production and profitability. Additionally, aquatic animal health professionals, aquatic animal health specialists and aquaculturists are increasingly aware of the need to use veterinary medicines responsibly and, to avoid the development of AMR in human pathogens and not treat aquaculture species with antimicrobial agents that are important to human medicine.

3.2 Use of veterinary medicines in aquaculture

In terrestrial and aquatic animal production systems, veterinary medicines are used for disease prevention (vaccines), as therapeutants (antimicrobial agents and antiparasitics) and for husbandry purposes (anaesthetics for handling, hormones to enhance reproduction and production, and disinfectants). Unlike in the farming of terrestrial animals, in aquaculture the number (more than 500) and diversity of species cultured (finfish, crustaceans, amphibians, molluscs, other invertebrates, seaweeds), the lack of information on efficacy and safety for many species, and the relatively small production levels for some species often result in limited interest by pharmaceutical companies to invest in costly product development and registration.

In aquaculture, as in other animal production sectors, veterinary medicines are used mainly to prevent and treat disease. In aquaculture, antimicrobial agents are typically applied either mixed in medicated feed or as bath treatments. Populations of aquatic animals requiring antimicrobial treatment typically contain some individuals that are healthy and feeding well, and others that are infected and may show clinical signs of disease, including reduced feeding. In aquaculture, the most common practice is metaphylactic treatment, which is a group-medication procedure that endeavours to treat diseased animals while medicating others in the group to prevent disease. The

use of antimicrobial agents as growth promoters is a phenomenon of land-based agriculture, where subdosing with antimicrobial agents improves growth and feed conversion by decreasing the gut mass and increasing absorption of nutrients (Hernández, 2005). However, there are no data demonstrating that these effects are seen in aquatic animals, and the use of antibiotics as growth promoters is not thought to play a significant role in aquaculture (Smith, 2012).

The enormous gains in aquaculture production capacity that have been achieved globally during the past 30 years would not have been possible without the use of veterinary medicines. As in other veterinary applications, antimicrobial agents in use in aquaculture are also used in human medicine. There are no antimicrobial agents that have been specifically developed for aquaculture use, and simple economic considerations suggest that this may remain the case.

The use of veterinary medicines has been taken up progressively by the aquaculture industry as the understanding of their use in health management and biosecurity has improved. However, veterinary medicines have not always been used in a responsible manner. During the past decade, the number of fisheries and aquaculture product refusals and detentions by major importing countries due to the presence of biological and chemical hazards has increased (see, for example, Koonse, 2016). For example, since 2001, the detection of the antimicrobial chloramphenicol in internationally traded shrimp has caused much concern (see, for example, Hanekamp, Frapporti and Olieman, 2003). This has resulted in a slowdown of imports, causing economic losses among producers and their governments. As a result, many governments have introduced changes or tightened national regulations on the use of antimicrobial agents.

While chemotherapy is likely to remain an important tool for controlling aquatic animal diseases, there is increasing recognition of its limitations. The emergence of vaccines has dramatically reduced dependence on antimicrobial agents in some sectors of aquaculture. In other cases, rather than providing a solution, chemotherapy may complicate health management by triggering toxicity, resistance, residues and occasionally, public health and environmental consequences. In

addition, the efficacy of some veterinary medicines under the conditions found in certain aquatic environments is questionable, both with respect to meeting treatment goals and regarding the potential environmental and socio-economic costs of unpredicted effects.

Maintaining animal health under culture conditions requires the availability of effective antimicrobial agents to increase population survival rates, reduce sequelae from infections, and improve FCRs. Without the use of veterinary medicines, aquaculture food production would be impaired. Rather than further restrictions, more judicious use of veterinary medicines by aquaculturists, better enforcement of current regulations by government and improved health extension support to the farmers would result in a more prudent and responsible use of veterinary medicines in aquaculture development.

3.3 Benefits of the use of veterinary medicines

The primary benefit of the use of veterinary medicines in aquaculture, as in the commercial livestock and poultry sectors, is that their prudent and responsible use supports the development of intensive, industrial-scale food production systems. They are needed to achieve the greatest production outputs for society and the most financial gains for investors through increasing the efficiency of production by minimizing the resources (land, water, feeds, etc.) required to produce a unit of aquatic food. The use of veterinary medicines is essential to modern agricultural production (including aquaculture), through improved on-farm biosecurity and husbandry (e.g. via the use of vaccines and disinfectants) and for the treatment of diseases that lead to reduced production (e.g. reduced growth, lower FCRs and decreased survival). In addition, veterinary medicines are indispensable for the treatment of epizootic disease outbreaks having the potential to cause mass mortalities, the failure of individual aquaculture enterprises and the occasional collapse of entire industries. Veterinary medicines have proved particularly useful in aquaculture situations (see COFI, 2017) involving:

- *New species culture development.* In the development of culture techniques for new species, there is often a lag phase between the identification and characterization of pathogens and the

development of disease control procedures. In such cases, the selective use of veterinary medicines may be necessary to ensure the viability of the new species until alternative control measures can be incorporated into production and health management programmes.

- *Failure of preventive measures.* The use of preventive measures such as good husbandry and vaccination does not always ensure the success of an aquaculture enterprise. Cultured aquatic animals subjected to stresses above what they are capable of enduring may develop depressed immune systems and compromised nonspecific barriers (e.g. skin), enhancing susceptibility to infections by pathogens that may only be resolved by the use of veterinary medicines.
- *Emerging and re-emerging infectious disease.* Globalization of trade and the increased ease with which live aquatic animals are moved between countries and regions of the world has led to a corresponding increase in the occurrence and importance of TAADs as causes of mass mortalities in aquaculture production. In such instances, the use of veterinary medicines to treat infections assists other biosecurity measures (e.g. diagnostics, health certification, quarantine, disease surveillance and emergency response, including eradication) to restrict the geographical spread of infections.
- *Changes in culture and environmental conditions.* Use of recirculation technologies, elevated growing temperatures, higher in-tank densities, chronic AMU to control diseases and high concentrations of farms in limited geographic areas may all change the manner in which pathogens and cultured species interact. In such instances, diseases may manifest themselves in novel ways, requiring rapid diagnosis and treatment using veterinary medicines.
- *Animal welfare.* Animal welfare issues are of increasing importance in both terrestrial and aquatic animal production systems. The use of veterinary medicines to treat disease outbreaks in aquaculture enterprises is often necessary for the well-being of the animals in question.

The responsible use of antimicrobial agents is an important part of farm biosecurity, as this helps ensure that pathogen challenges are minimized, that the natural defence mechanisms of the cultured stocks are maximized, and that disease and mortality, including costs of containing, treating and/or eradicating diseases, are reduced. The injudicious and/or incorrect use of antimicrobial agents poses a great concern to successful and sustainable aquaculture (Bondad-Reantaso, Arthur and Subasinghe, 2012).

3.4 Issues concerning use of veterinary medicines

Concerns over the use of veterinary medicines in aquaculture include: (i) disease diagnostics issues; (ii) human and animal health issues resulting from misuse; (iii) environmental/ecological issues; and (iv) legislative and enforcement issues.

- *Disease diagnostics issues.* These center around the need for aquaculturists and aquatic animal health professionals to have rapid and accurate diagnoses of pathogens prior to initiating treatment using veterinary medicines. For antimicrobial agents in particular, there is also the need to promote the use of susceptibility testing, using internationally standardized protocols to ensure that the antibiotic applied will be effective against the strain of pathogen causing the disease outbreak.
- *Human and animal health issues.* While the main concern for animal health is treatment failure due to an increase in resistance, the adverse health effects that might occur in human populations are those associated with the presence of residues in food products or with the development of resistance in bacteria associated with human disease. AMR and residues of banned substances in product were identified by the 2006 Joint FAO/OIE/WHO Expert Meeting on Antimicrobial Use and Antimicrobial Resistance in Aquaculture (see WHO/FAO/OIE, 2006) as important hazards. AMR may arise either directly via enrichment for these bacteria in the aquaculture environment or indirectly via the enrichment for genes that encode such resistance, and which may subsequently be transferred to bacteria associated with human disease. Another principal concern is the degree that

residues in aquaculture products may affect human health by either: i) exerting a selective pressure on the dominant intestinal flora; ii) favouring the growth of microorganisms with natural or acquired resistance; iii) promoting, directly or indirectly, the development of acquired resistance in pathogenic enteric bacteria; iv) impairing colonization resistance; or v) altering metabolic enzyme activity of the intestinal microflora. The risk to human health due to the presence of antimicrobial residues in food products is evaluated as part of the authorization procedure for veterinary drugs. If present in concentrations above the established MRLs, residues can present a hazard to consumers of fish and shellfish produced in aquaculture. Some of the most publicized toxic effects of residues are those caused by chloramphenicol and by residues leading to drug allergies.

- *Environmental/ecological issues.* Environmental/ecological issues relating to the use and misuse of veterinary medicines include the release of medicines into the aquatic environment through leaching from unconsumed feeds, intentional/unintentional release of effluent waters from aquaculture facilities and the presence of residues in faecal materials. Impacts on local ecosystems are in general poorly studied but include concerns about accumulation of residues in sediments and impacts of drugs and chemicals on natural biota, including possible development of AMR in aquatic bacteria.
- *Legislative and enforcement issues.* Countries need to have in place appropriate policies and well-conceived legislation and regulations regarding the use of veterinary medicines in aquaculture, including aspects such as procedures for registering medicines for use in aquaculture production; licensing of aquatic animal health professionals; extra-label use; and record keeping by manufacturers, aquaculture production facilities and aquatic animal health professionals. Countries must also have the trained workforce and infrastructure necessary to enforce legislation and regulations, with appropriate penalties for violations.

3.5 Addressing the problem of AMR

AMR refers to microorganisms – bacteria, fungi, viruses and parasites – that have acquired resistance to antimicrobial agents, e.g. antibiotics. While this phenomenon can occur naturally through microbial adaptation to the environment, it has been exacerbated by inappropriate and excessive use of antimicrobial agents.

Various factors are involved, such as: i) lack of regulation and oversight of use; ii) poor therapy adherence; iii) non-therapeutic use; iv) over-the-counter or internet sales; v) availability of counterfeit or poor-quality antimicrobial agents and; (vi) the use of antimicrobial therapy to control diseases in cases where any microbiological role is secondary or opportunistic due to environmental factors majorly affecting aetiology. The consequences of AMR include the failure to treat infections successfully, leading to increased mortality; more severe or prolonged illness; production losses; and reduced livelihoods and food security. The indirect impacts of AMR include higher costs for treatment and health care (FAO, 2016a).

Antimicrobial agents are important to the overall implementation of effective biosecurity; however, they need to be used more carefully. This can be tackled through, for example:

- *Effective policies and legislation.* Countries need to have in policies, legislation and regulations concerning the prudent and responsible use of antimicrobial agents in aquaculture that are appropriate, well-conceived and effectively enforced, including aspects for the registration of antimicrobial agents and licencing of aquatic animal health professionals and others.
- *Improved knowledge base.* Knowledge in key areas such as such as diagnosis, surveillance, risk analysis, and disease prevention, control and management should be improved.
- *Improved capacity building.* This includes capacity building at all levels of the aquaculture production chain to promote the responsible use of antimicrobial agents, such as improved extension; better aquaculture and biosecurity practices; and more effective diagnostics that prevent disease occurrence in

the first place. Countries must also have appropriately trained workforce and essential infrastructure to enforce legislation, including appropriate penalties for violation.

- *Improved public–private-sector partnerships.* Cooperation between government, the private sector and academia should be promoted, because dealing with disease should be a shared responsibility among all players in the value chain. The involvement of all stakeholders is critical to efforts to reduce the need for the use of antimicrobial agents.

The Global Plan of Action on AMR (with contributions from FAO and the World Organisation for Animal Health, OIE) was adopted during the 68th World Health Assembly in May 2015 (WHO, 2015). The World Assembly of the OIE delegates in May 2015 adopted the strategy (OIE, 2016), and the 39th FAO Conference (June 2015) adopted Resolution 4/2015 (FAO, 2016b). A political declaration was made during a high-level meeting on AMR at the 71st United Nations General Assembly (UNGA, September 2016). The UNGA called upon the Tripartite (i.e. FAO as global leader for food and agriculture, the OIE as global leader for animal health and welfare and WHO as global leader for human health) and other intergovernmental organizations to support the development and implementation of NAPs and AMR activities at the national, regional and global levels under the One Health platform. The FAO, OIE and WHO agreed to step up joint action to combat health threats associated with interactions between humans, animals and the environment (FAO, 2018a). A memorandum of understanding was signed in May 2018 to strengthen their long-standing partnership, with a strong focus on tackling AMR. In addition, the United Nations Secretary-General convened the Interagency Coordination Group (IACG) on AMR in May 2017 in consultation with Tripartite members to provide guidance on approaches for ensuring sustained global action on AMR, and report back to the Secretary-General during the 73rd General Assembly in 2019. This mandate included making recommendations on enhancing coordinated action across sectors and countries, building political momentum, future governance and mobilizing stakeholders.

A joint Tripartite workplan for 2019–2020 was developed with five focus areas to be achieved through multisectoral collaboration, such as: 1) implementation of the NAP on AMR; 2) awareness and behaviour change; 3) surveillance and monitoring of AMR and AMU; 4) stewardship and optimal use of antimicrobial agents; and 5) monitoring and evaluation. The joint workplan also recognized the need for UNEP to join this collaboration. Furthermore, a multi-partner trust fund (MPTF) to secure consistent and coordinated financing for a five-year period was established by the Tripartite, and administered by the United Nations Multi-Partner Trust Fund Office. Resources will be prioritized to support NAPs and implement the Tripartite workplan in coordination with UNEP.

The FAO Action Plan on Antimicrobial Resistance 2016–2020 (FAO, 2016a) supports the implementation of Resolution 4/2015. It addresses four major focus areas:

- Awareness: improve awareness on AMR and related threats
- Evidence: develop capacity for surveillance and monitoring of AMR and AMU in food and agriculture
- Governance: strengthen governance related to AMU and AMR in food and agriculture; and
- Best practices: promote good practices in food and agricultural systems and the prudent use of antimicrobial agents

The human-animal-ecosystem interface (HAEI), which encompasses all direct and indirect human exposure to animals and animal products and to the environment shared by all, leads to health threats that pose risks to public health, animal health and global health security. This complicated interface requires a holistic and multisectoral “One Health” approach, as AMR cannot be effectively addressed by one sector alone. The FAO/OIE/WHO Tripartite Collaboration is an important mechanism towards collective actions to minimize the emergence and spread of AMR. The Tripartite collaboration is aimed to:

- ensure that antimicrobial agents continue to be effective and useful to cure diseases in humans and animals;
- promote prudent and responsible use of antimicrobial agents; and
- ensure global access to medicines of good quality.

In aquaculture, there are several strategies that may reduce or eliminate AMR. These include avoidance using clean facilities, use of immunostimulants to enhance innate immunity, inclusion of probiotics in feeds, vaccination, phage therapy via feeds and the use of plant extracts. Of these, vaccines have been widely used against fish infections. Nanoparticles may be used to deliver vaccines in the future. Avoidance of AMR can also be achieved by the farming of high-value SPF species in non-organic artificial environments which can be disinfected, using ultraviolet (UV) treated inflow water, thus preventing contact with resistant bacteria in the farm environment. More knowledge and research are needed in order to better understand the successes and failures, cost implications, efficacy, practicality (especially for small-holders), adverse effects on the farm environment, and how such alternatives improve health and enhance host immunity. Alternatives to antimicrobial agents such as the use of probiotics and plant extracts should be continuously explored.

4. RECOMMENDATIONS FOR THE PRUDENT AND RESPONSIBLE USE OF VETERINARY MEDICINES IN AQUACULTURE

4.1 Recommendations to government

States, through their national competent authorities and other relevant agencies should consider the following actions:

1. Implement, incentivize, support and enforce GAqPs, including their legal regulatory structure, environmental conditions, etc. Such programmes should include measures to reduce the need for therapeutic interventions, ensure proper record keeping of use of therapeutic agents, and assure there are no unacceptable levels of therapeutic agents in aquaculture product or the receiving environment.
2. Develop and implement the national GAqP programme. Officers should be trained in GAqPs and should conduct inspections of farms to assure that GAqPs are being properly implemented (e.g. proper densities are being maintained, waste water is not impacting source water, farms and hatcheries are keeping drug use records, samples are being collected and tested, etc.).
3. Consult relevant private-sector stakeholders, including NGOs, in a transparent manner, in line with international standards and guidelines, when making laws and regulations.
4. Consider, urgently, developing alternative approaches to the elaboration of MRLs for veterinary medicines used in aquaculture species – in order to facilitate trade in safe food.
5. Encourage the development of data to support the registration and recognition of appropriate food safety standards (e.g. MRLs) for veterinary medicines used in aquaculture production.
6. Promote efforts that improve the selection and use of appropriate feeds, feed additives and medicated feed stuffs.

7. Establish a clear regulatory framework for the registration, inspection and surveillance of veterinary medicines, including a clear definition of the role and responsibilities of the competent authority for such tasks. National standards should be in line with international standards and guidelines to ensure safety and effectiveness.
8. Develop the technical capacity and infrastructure needed to enforce existing regulations, as effective enforcement is critical for implementation of laws and regulations related to the prudent and responsible use of veterinary medicines. This includes the capacity and infrastructure needed to control the importation, commercialization and use of veterinary medicines in aquaculture production and for the inspection of aquaculture products for antibiotic residues.
9. Encourage the development of government-sponsored support and antimicrobial susceptibility testing services in those areas that have no consultative services or where the size/type of industry is such that a diagnostic service cannot be self-supporting, recognizing that an accurate diagnosis is essential to the proper application of antimicrobial therapy.
10. Ensure diagnostic support to the aquaculture sector with specialists able to diagnose diseases in the field and through a network of national and regional laboratories with competent staff and equipment that can address the environmental conditions of aquatic animals and their pathology, parasitology, microbiology, antimicrobial susceptibility, residue analysis and water analysis. The use of new communication technologies should be optimized to inform all those involved in the disease response.
11. Actively encourage the development, dissemination and adoption of internationally standardized protocols for antimicrobial susceptibility testing and consensus criteria (epidemiological cut-off values) for the interpretation of the data they generate.

12. Disseminate accurate information for when and how to apply veterinary medicines properly, beginning with an understanding of the environmental conditions under which aquatic animals are reared, an accurate diagnosis of the disease and identification of the causative agent and the antimicrobial susceptibility of that agent. This information should be used with a thorough understanding of the aquatic animal being reared, the biological and production system in which it is being reared and the intended purpose of the aquaculture product.
13. Actively promote the adoption of accreditation systems for diagnosticians and diagnostic laboratories.
14. Establish an international system of inter-laboratory comparisons (ring tests) to harmonize and ensure the quality and accuracy of disease diagnostic testing.
15. Establish active and passive surveillance on residues, AMU and AMR, and diseases in aquaculture. AMR should be determined using internationally standardized susceptibility testing protocols and the application of consensus-based, internationally harmonized epidemiological cut-off values (see no. 11).
16. Consider the role of aquaculture together with AMU and misuse in human medicine and terrestrial animal agriculture when assessing the contribution of antimicrobial agents to environmental reservoirs of resistant human pathogens.
17. Develop and maintain a record-keeping system for the distribution chain of veterinary medicines used in aquaculture. Such a system should cover registration, manufacturer inspection, import, retail sale and handling/use by farmers. Competent authorities and collaborating mechanisms should be clarified to ensure the effectiveness of the system. Capacity-building activities should be identified and conducted to support relevant stakeholders in the distribution chain, particularly the farmers. Where appropriate, cooperation with international/regional organizations and the private sector should be promoted.

18. Establish and/or improve biosecurity systems at several levels (international, national, regional and individual farm/production system/farm cluster) as appropriate for prevention and response (control and eradication of) to disease.
19. Develop and maintain an information system supporting the prudent use of veterinary medicines and the improvement of biosecurity in aquaculture. Such an information system should include, among others, information on veterinary medicines that can be used in aquaculture and guidelines for their prudent use, the application of biosecurity in aquaculture, and rapid alert on disease outbreaks and the current situation with respect to AMR.
20. Develop aquatic animal health extension services, as appropriate, in collaboration with producers' associations, where they exist, that include mechanisms to promote the prudent and responsible use of veterinary medicines in aquaculture production systems.
21. Establish and foster communication and networking among stakeholders at all levels to support the prudent use of veterinary medicines and the improvement of biosecurity in aquaculture.
22. Work with and train farmers on GAqPs/BMPs, including the judicious use of veterinary medicines, sanitary management, biosecurity and diagnostics.
23. Provide increased resources for research in the aquaculture sector and aquatic animal health, with emphasis on disease prevention; the efficacy and safety of veterinary medicines in different environmental conditions; the environmental impacts and alternatives to the use of antimicrobial agents; and methodologies for active and passive surveillance on residues, AMU and AMR, and diseases in aquaculture.
24. Embrace the "One Health" platform and establish systems for communication and cooperation between the areas of human medicine, veterinary medicine, and aquaculture, agriculture and other industries.

25. Consider implementing a “polluter pays principle” in cases where irresponsible use of a veterinary medicine by a producer causes serious negative social, economic or environmental impacts.

4.2 Recommendations to the private sector, especially small-scale aquafarmers

The private sector, including small-scale aquaculture producers, drug manufacturers, input and service providers, and other stakeholders in the value chains, should consider the following actions:

1. Adhere to relevant government laws, regulations and policies pertaining to the prudent and responsible use of veterinary medicines in aquaculture.
2. Implement responsible farming through GAqPs based on effective biosecurity measures, as this practice will:
 - a. minimize disease occurrence (and consequently outbreaks) – this should be the baseline and normal husbandry practice;
 - b. lessen the need for and use of therapeutic agents; and
 - c. reduce the development of AMR.
3. Create an effective health monitoring and reporting system to manage sanitary risks proactively to prevent disease outbreaks. This includes quality assurance of all inputs to the farm (e.g. the introduction of fish and eggs), and the continuous monitoring of aquatic animal health with early reporting of disease to the competent authorities as well as neighbouring farms.
4. Have access to qualified (trained and licensed) personnel that can perform diagnoses and prescribe and use veterinary medicines.

5. Raise awareness among farm personnel on the need for veterinary medicines to be used in a prudent and judicious manner, the relevant practices and techniques and their correct implementation.
6. Keep records on the sale of veterinary medicines (drug sellers) and what veterinary medicines are used (by farmers) to provide data to competent authorities and other legitimate users and for future use in epidemiological investigations.
7. Be conscious of available extension agents and services that can provide knowledge and guidance on sustainable aquaculture practices.
8. Be aware of opportunities to increase their representation in the industry through forming associations and clusters in order to:
 - create a platform to increase their participation and influence in the industry decision-making processes;
 - pool resources to both learn and share knowledge about sustainable production systems and how they should be implemented;
 - be aware that that they can, and should, contribute to government's efforts in making laws and regulations in a transparent, inclusive manner in line with international standards;
 - cooperate with government, NGOs and other experts to establish a consensus of sustainable production systems and industry standards; and
 - encourage governments to create appropriate incentives for small-scale producers to minimize the use of veterinary medicines in aquaculture production.

4.3 Recommendations to aquatic animal health professionals and specialists

The following section draws heavily on the principles and guidance for aquatic veterinarians provided by Smith *et al.* (2008), the United States Food and Drug Administration (USFDA) (2009), Matyszczak and Prater (2012), Smith (2012) and the OIE *Aquatic Animal Health Code* (2018a). Readers are referred to these documents for more detailed information.

When possible, those responsible for making prescriptions should be the same people responsible for making the diagnosis. In cases where this is impossible, those making prescriptions and those making diagnoses should work closely and consult one another.

Aquatic animal health professionals and aquatic animal health specialists who have training in the principles of aquaculture health management are extremely important resources for producers. Aquatic animal health professionals and specialists should consider the following recommendations:

1. Provide practical services to the aquaculture industry; among others, these should include responding to producers' questions, conducting on-farm interventions during disease outbreaks, making recommendations on therapeutic options, and providing important information concerning regulations, their application and their importance.
2. Accept responsibility for helping aquaculture producers design biosecurity, management, immunization, production unit and nutritional programmes that will reduce the incidence of disease and the need for the use of veterinary medicines.
3. Be aware that the environment of the host always plays a role in the aetiology of diseases. Antimicrobial therapy is unlikely to be prudent or effective in polymicrobial diseases and when microorganisms play a secondary or opportunistic role in situations where poor environmental conditions or poor husbandry play a dominant role in disease aetiology.

4. Consider the use of other therapeutic options prior to selecting antimicrobial therapy. The responsible use of antimicrobial agents should be a component of other good production practices such as the implementation of biosecurity measures, the utilization of vaccines, nutritional optimization, husbandry changes, and other elements of a successful disease prevention programme.
5. Use antimicrobial agents only within the confines of a valid professional client-patient relationship, including both the dispensing and issuing of prescriptions and veterinary feed directives.
6. Only dispense antimicrobial agents on prescription (issued by an appropriately licensed aquatic animal health professional) in accordance with national legislation.
7. Properly select and use veterinary medicines based on available laboratory reports, label (including package insert) information, additional data in the literature and consideration of the pharmacokinetics, spectrum of activity and pharmacodynamics of the drug, with due consideration for the OIE principles for responsible and prudent use of antimicrobial agents in aquatic animals (see OIE, 2018a).
8. Implement surveillance programmes that include antimicrobial susceptibility testing and develop treatment and control protocols for each aquaculture industry.
9. Have strong clinical evidence of the identity of the target microorganism based upon history, clinical signs, necropsy, laboratory data and/or past experience before recommending treatment with veterinary medicine.
10. Treat foodfish with veterinary medicines according to the product label recommendations (including indication, dosage, duration, fish species, withdrawal periods and environmental conditions).

11. Use antimicrobial agents with a specific clinical outcome(s) in mind, including a specific target for population morbidity and/or mortality rate reduction.
12. Limit therapeutic antimicrobial treatment to ill or at-risk animals, treating the fewest animals indicated.
13. Avoid treatment of secondary infections if the primary cause of disease is still present.
14. Where possible, establish an antibiogram or sensitivity pattern for the target pathogen. In its absence, the choice of veterinary medicine can be based on previous applications, history of antibiograms in previous isolations, drug availability and economics.
15. Determine pathogen susceptibility to antimicrobial agents (antimicrobial sensitivity testing/antibiogram) using internationally standardized testing protocols at the first indication of increasing morbidity or mortality of a production animal population and monitor the therapeutic response to detect changes in microbial susceptibility and to evaluate antimicrobial selections.
16. Avoid the indiscriminate use of veterinary medicines by using products that have the narrowest spectrum of activity and known effectiveness *in vivo* against the pathogen causing the disease problem.
17. Choose antimicrobial agents of lesser importance in human medicine and do not choose an antimicrobial agent for which emergence of resistance is expected to be in an advanced stage. Antimicrobial agents important in human medicine should be used only after careful review and reasonable justification; such antimicrobials must be approved for use in foodfish production.

18. Avoid repeated treatment of a population of cultured animals with the same antimicrobial agent. Instead, preventive measures based on improved husbandry, biosecurity and vaccination should be encouraged to avoid disease outbreaks.
19. Strive to attain a complete administration of a therapeutic dose of medication to the infected animals.
20. Apply waste recuperation techniques such as sedimentation or filtration to reduce the quantity of antimicrobial agents released to receptor watersheds.
21. Avoid oral administration of veterinary medicines to affected populations, as affected populations are typically inappetent.
22. Use, whenever possible, a veterinary medicine that is labelled to treat the condition diagnosed and licensed for use on the species to be treated. Where extralabel use is necessary, professionals should use a veterinary medicine licensed for other food-producing species and should ensure that application is consistent with national regulatory agency laws, regulations and policies. In such cases, an application of a minimal withdrawal period of at least 500 °C d is recommended.
23. Do not (i) use combination antimicrobial agent therapy (polypharmacy) unless there is information to show that this decreases or suppresses target organism resistance development, (ii) use compounded antimicrobial agent formulations, (iii) use antimicrobial agents to treat cases with a poor chance of recovery or iv) use antimicrobial agents prophylactically.
24. Ensure proper on-farm drug use and protect the integrity of veterinary medicines through proper handling, use of protective personnel equipment (e.g. gloves and masks), storage and observation of the expiration date.

25. Minimize environmental contamination with veterinary medicines by ensuring their proper disposal or, where possible, their return to pharmaceutical distributors.
26. Prescribe, dispense or write a Veterinary Feed Directive for drug quantities appropriate to the production-unit size and expected need using the approved formulation.
27. Work with producers and/or facility aquatic animal health management personnel to ensure that farm personnel achieve adequate understanding on the use of veterinary medicines, including indications, diagnosis, dosages, withdrawal times, route of administration, storage, handling and accurate record keeping (i.e. date, diagnosis, prescribed veterinary medicine, duration of treatment, number of animals treated, withdrawal time implemented).
28. Work closely with all other aquatic animal health experts involved in population health management at the production facility.
29. Participate in continuing education programmes that include therapeutics and emergence and/or development of AMR.

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These Technical Guidelines on Prudent and Responsible Use of Veterinary Medicines in Aquaculture are developed to support sections of the Code addressing responsible fisheries management (Article 7), aquaculture development (Article 9), international trade (Article 11) and fisheries research (Article 12). They also support the OIE international aquatic animal health standards and the FAO/WHO Codex Alimentarius food safety standards. Safe and effective veterinary medicines are essential to efficient commercial aquaculture production, and their use should be in line with established principles on their prudent use to safeguard public and animal health. There is a need to establish and maintain appropriate legal and administrative frameworks that facilitate responsible aquaculture development; promoting better management practices/good aquaculture practices favouring preventative hygienic measures; and developing and formalizing NSAAH and health management procedures, adhering to international standards that incorporate mechanisms for the prudent and responsible use of veterinary medicines. These Technical Guidelines support the FAO/OIE/WHO Tripartite Collaboration towards collective actions within the 'One Health' approach to minimize the emergence and spread of AMR.

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