Global perspective on Antimicrobial Usage (AMU) and Antimicrobial Resistance (AMR) in Aquaculture

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Food and Agriculture Organization of the United Nations (FAO)
Very complex interface: different productions systems and sectors involved: aquatic, terrestrial, environment.

14 sectors
- Finfish
- Crustaceans
- Mollusks
- Dairy
- Beef
- Sheep, mutton and lamb
- Goat
- Swine
- Poultry – layers
- Poultry – broilers
- Turkey
- Rabbit
- Fruit
- Crops
  - Legumes
  - Grains
  - …

- Smallholder farms
- Medium commercial operators – local markets
- Intensive, large commercial entities – national and international scope
One Health at FAO

Inter-departmental Working Group chaired by FAO CVO

Multidisciplinary expertise: animal health, livestock and production, food and feed safety, plant health and production, fisheries and aquaculture, legislative contexts, etc.) - needed to address a cross-sectoral issue such as AMR.

Each of these aspects were considered in developing the FAO Action Plan (in support of Global Action Plan on AMR) and implementation at national and regional levels.
Issues identified

• Regulatory framework for authorization of aquatic veterinary medicines:
• Control on the distribution and use of veterinary medicines:
• Technical assistance and capacity building
• International standards and harmonization of methodologies
• Risk assessment for the most significant aquatic pathogens;
• Develop methodologies and plans for monitoring sediment, water, animals and other carriers
• Need for more globally recognized MRLs for aquaculture drugs
• Lack of harmonized residue methods for aquaculture;
• Lack of globally recognized requirements for drug prescription standards;
• Current requirements for seafood health certificates do not adequately address aquatic animal health problems;
• Requirement of traceability standards favours large companies over small companies; and
• Lack of traceability system impairs the ability to trace back inappropriate drug use to the farm level.

Provides guiding principles, and recommendations for governance authorities, producer sector and aquatic health professionals
**New species culture development:** lag phase between identification and characterization of pathogens and the development of disease control procedures; use of vet medicines to ensure viability of the new species until alternative control methods can be incorporated into production and health management programmes.

**Failure of preventive therapy:** good husbandry & vaccination not always ensure successful aquaculture. When exposed to stress above what they are capable of enduring, animals may develop depressed immune systems and compromised nonspecific barriers (e.g. skin), enhancing susceptibility to infections by pathogens that can only be resolved by the use of antimicrobials.

**Emerging and re-emerging infectious disease:** Number & occurrence of transboundary diseases have increased and the use of vet medicines to treat such infections supports other biosecurity measures to restrict the geographical spread of infections.

**Developing culture technologies:** Use of recirculation technologies, elevated growing temperatures, higher densities, chronic antimicrobial usage to control diseases and higher concentration of farms in limited geographical areas - may all change the manner in which pathogens and cultured species interact; diseases may manifest themselves in novel ways, requiring rapid diagnosis and treatment with antimicrobials.
Concerns on the use of veterinary drugs

Abuse, overuse, misuse: Should only be used in a confirmed bacterial infection case; not for viral infection; thus based on correct diagnosis. Only antimicrobials labelled to treat the condition diagnosed and licensed for use of the species affected should be used; properly handled (and disposed), stored and expiry dates should be closely monitored; and they should be administered by a recognized and/or licenced aquatic animal health professional.

Human & animal health issues: Animal health issue: treatment failure due to increase in resistance. Human health issue: adverse health effects associated with the presence of residues in the food produced or resistance in bacteria associated with human disease. Resistance in bacteria causing human disease: directly via enrichment of these bacteria in the aquaculture environment or indirectly via enrichment of the genes that encode such resistance and which may subsequently be transferred to bacteria associated with human disease.

Environmental & ecological issues: Release through leaching from unconsumed feeds, intentional or unintentional release of effluent water from aquaculture facilities and presence of residues in faecal materials. The ecological concerns include accumulation of residues in the sediments, impacts of drugs and chemicals on natural biota, and possible development of AMR in aquatic bacteria.

Joint FAO/OIE/WHO Expert Meeting on Antimicrobial Use and Antimicrobial Resistance in Aquaculture: two main hazards: residues and resistance
FMM/RAS/298/MUL: Strengthening capacities, policies, and national action plans on prudent and responsible use of antimicrobials in fisheries

- 92 participants from 14 countries representing intergovernmental organizations, academe, research institutions, government and the private sector,
- 67 technical and country experience presentations and 12 technical working group discussions, the participants in these three regional workshops were provided:
  (i) increased awareness, knowledge and skills;
  (ii) preliminary guidance in the conduct of antimicrobial use (AMU) and antimicrobial resistance (AMR) surveillance;
  (iii) opportunities for intensive exchange of information between country nationals and experts;
  (iv) a venue for better understanding of country situations with respect to aquaculture biosecurity status, AMR-related activities and ongoing actions;
  (v) overall guidance in the development of the aquaculture component of country NAPs on AMR and the integration of the aquatic component.

Contains a comprehensive list of important bacterial pathogens in aquaculture production
### Preliminary guidance considerations in the conduct of AMU and AMR surveillance

<table>
<thead>
<tr>
<th>1. Contact information profile</th>
<th>2. Farm information</th>
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<tbody>
<tr>
<td>3. <strong>Types</strong> of antimicrobial agents used in cultured species (antibiotics, external treatments, antihelminthics)</td>
<td>7. <strong>Availability</strong> of these agents (freely available, prescription)</td>
</tr>
<tr>
<td>4. <strong>Doses</strong> of antimicrobial agents used in cultured species, expressed in mg</td>
<td>8. <strong>Drug sales</strong></td>
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<tr>
<td>5. <strong>Duration</strong> of antimicrobial agents used in cultured species, expressed in days</td>
<td>9. Drug sales by <strong>routes of administration</strong> (e.g. medicated feed; bath treatment; directly to the pond; etc)</td>
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<tr>
<td>6. <strong>Effectiveness</strong> of antimicrobial agents used in cultured species, expressed in percent</td>
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**Data collection of data (consideration)**
- Antimicrobial classes included on the list are based on a previous analysis of the current known national antimicrobial resistance mechanisms.
- Nomenclature of antimicrobial agents reported should comply with international standards.
- If the report is going to be available to the public, anonymity of individual enterprises should be ensured.

**Logistics/operational aspects (considerations)**
- Information to be collected by government officers, extension officers, academic institutions.
- Resources for survey should be made available by the authorities.
- Stakeholders: farmers, veterinarians/aquatic health professionals; associations of aquaculture producers, exporters; aquaculture extension officers; academic institutions; pharmaceutical industry, customs department; fish inspectors; government officers.
Surveillance objectives (examples)

• Establish baseline data on AMU and AMR in country for important cultured aquatic animal species.
• Identify data gaps and research requirements.
• Conduct risk analyses as relevant to aquatic animals in a One Health approach.
• Identify appropriate interventions to control the emergence and spread of resistant bacteria including prudent use guidelines and evaluate their effectiveness.
• Provide recommendations on aquatic animal health policies and programmes.

Sampling design (considerations)

• Sampling to cover aquaculture farm animals, animals in retail, processed products.
• Random sampling to cover all aquaculture species and ecological regions with aquaculture activity in the country.
• Targeted sampling based on information on AMU.
• Samples should be representative of the AMR situation in the concerned aquaculture system and cultured fish/shrimp species.
• Continuous sampling (longitudinal) to cover seasonal and regional variations.
Target microorganisms (considerations)

- Bacteria that are native to the aquatic environment in the ecosystem (freshwater, marine, brackish water).
- Pathogens relevant to the aquaculture species in the culture system in the country.
- Indicators of contamination coming from humans and animal farms.
- Human pathogens like *Salmonella*, if there has been an established link between the aquaculture system and outbreaks of fish poisoning.
- Number of isolates of each type to be tested based on frequency of isolation of the target microorganism and expected level of prevalence of resistance in the bacterial population.

Laboratory methodology (considerations)

- Use internationally valid methods for isolation and identification of target bacterial species (e.g. International Organization for Standardization (ISO), AOAC International, American Public Health Association).
- If such methods are not available, consider “fit for purpose” method based on performance characteristics of the method (e.g. FAO/WHO Guidance on human pathogenic *Vibrio* spp.).
- Perform disc diffusion and MIC assays as per CLSI or other internationally validated guidelines.
- Ensure laboratory quality control systems are in place. Preferably, laboratories should have accreditation (e.g. ISO 17025).
- Conclusions on sensitivity/resistance should be based on epidemiological cut-off values.
- If these values do not exist, try to establish by analyzing MIC values of required number of wild-type isolates.
- Report results providing data on resistance, MIC and zone diameter values.
FMM/RAS/298/MUL: Strengthening capacities, policies, and national action plans on prudent and responsible use of antimicrobials in fisheries

<table>
<thead>
<tr>
<th>Topic</th>
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<tbody>
<tr>
<td><strong>Fish Waste Management</strong>: Turning Waste into Healthy Feed with Antimicrobial Properties</td>
<td>Practical Management of Bacterial Diseases in Finfish Aquaculture to Minimise AMR</td>
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<tr>
<td>Complexities Involved in Source Attribution of AMR Genes Found in Aquaculture Products</td>
<td>Review of National Residue Control Programme for Aquaculture Drugs in Selected Countries</td>
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<tr>
<td>Critical Review of Methods Used in Published Studies of Susceptibility of <em>Vibrio</em> spp.; Lessons to Be Learnt</td>
<td>EU’s Action Plan on AMR and Implications for Trading Partners with Example of National Action Plan for Croatia</td>
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<tr>
<td>Correct Diagnostics: Prerequisite for Prudent and Responsible Antimicrobial Administration</td>
<td>AMU and AMR in Aquaculture in the People’s Republic of China</td>
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<tr>
<td>Contact-Zoonotic Bacteria of Warmwater Ornamental and Cultured Fish</td>
<td>Country experiences in developing aquaculture component of NAPs on AMR: Malaysia, Philippines, Singapore and Viet Nam</td>
</tr>
<tr>
<td>Potential Transfer of AMR and Zoonotic Bacteria Through Global Ornamental Fish Trade</td>
<td>Guidance in Development of Aquaculture Component of a National Action Plan on AMR</td>
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17 papers based on technical presentations delivered during the three workshops; wide range of topics that will assist in better understanding antimicrobial resistance (AMR) in aquaculture.

https://www.asianfisheriessociety.org/publication/archivedetails.php?id=162&q=1
Aquaculture Component of National Action Plans (NAPs) on AMR

Among the top aquaculture producers: **positive findings**

- **9 countries** where aquaculture component of country NAP is in place
- **3 countries** where aquaculture component of country NAP is discussed
- **3 countries** where aquaculture component of country NAP is not discussed

80 NAPs (publicly available at WHO website)
Advocacy to support responsible and prudent use of antimicrobials in aquaculture and reduce AMR targeting Competent Authorities and farmers

Side Event during the FAO Committee on Fisheries (COFI) SubCommittee on Aquaculture 9th Session (October 2017, Rome)

Awareness raising activities on AMR for Indian fishfarmers, Nellore, June 2019.
18 experts shared their knowledge and points of view.
854 attendees for 2 days.

595 attendees for two days.
Provides a better and practical understanding of the interrelationship of the various elements at various levels (i.e. different levels in the aquaculture value chain) and best practices in aquaculture biosecurity to prevent diseases and/or minimize AMR.

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<tr>
<th>Know your fish</th>
<th>Maintain good husbandry</th>
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<tr>
<td>Know your system</td>
<td>Use antimicrobial prudently</td>
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<tr>
<td>Know you pathogens</td>
<td>Respect food safety</td>
</tr>
<tr>
<td>Know your contamination pathways</td>
<td>Respect the environment</td>
</tr>
<tr>
<td>Source healthy seed</td>
<td>Implement a biosecurity plan</td>
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</table>
• Using the 10-point best practice guidelines as a ‘biosecurity landscape’,
• Biosecurity activities and ‘risk mindset’ should be an everyday practice.
• Epidemiological triad: interaction between a pathogen and susceptible population in a suitable environment that allows transmission of the pathogen and development of disease in the population.
• The pathogen must be present for disease to occur, but its presence may not always result in disease.
• Risk sectors in the value chain!
• Recycling of resistance bacteria and antimicrobial resistance genes in the environment
• People important!

Karunasagar, 2012
Each species' risk profile to microbial pathogens.
Farmed aquatic animals = poikilothermic = body temperature and metabolic and physiological processes, in particular their ability to resist infection, depend on environmental temperature.
Microbial pathogens exhibit environmental preferences.
Unsuitable temperature, DO and other production stressors compromise the ability of aquatic animals to resist microbial pathogens.
Microbial susceptibility differs with the life stage of animals being cultured.
Persistence of infection in older life stages may underlie an increased susceptibility to secondary bacterial pathogens = particularly important as pathogens may coexist with their host without expression of symptoms.
• **Mixed infections** are common and need to be taken into consideration when developing treatment and control strategies.

• **Many bacterial pathogens are opportunistic,** thrive large dense populations - environments that are subject to husbandry, feeding and culture conditions that weaken the animals’ resistance.

• **Some bacterial species are obligate pathogens** that will cause disease irrespective of co-infections with other pathogens or enabling husbandry factors.

• **Endemic pathogens:** they occur widely in water bodies of a geographic region or country.

• **Exotic pathogens:** never been reported or have been shown through targeted surveillance to be absent from a region or country; generally important to trade & often governed by international standards requiring obligatory reporting.

• A change in a microbial pathogen as well as a switch to new host species = **emerging pathogen;** microbial pathogens that were not previously known to cause disease in a particular cultured species or in a particular geographic region.
• **Diverse production systems**: ponds, cages, tanks, raceways and RAS: depends on species cultured, life stage produced, geographic location, water availability and prevailing climatic conditions.

• **Water source**: the most critical component of any aquaculture system: borehole or well water used in RAS and hatcheries; stream or river water flowing into or through ponds, tanks and raceways; tidal flows into ponds; and lake and sea water for cages.

• **Intensification of water exchange** depends on the species; some will thrive in stagnant or semi-stagnant water, many require water exchanges and flow rates commensurate with the oxygen requirements and metabolic waste removal needs of the species.

• **Hazard Analysis and Critical Control Point (HACCP)** thinking allows the identification of risk hot spots in the value chain and corresponding biosecurity management.
• **Pathogens transfer readily through water**: water connectivity provides pathogen transfers between wild and farmed animals and *vice versa*.
• Spring or ground water generally regarded as free from pathogens. Other forms of water require some form of treatment, either chemical (ozonation) and/or physical (filtration and ultraviolet radiation) to render the water pathogen free.
• Some microbial pathogens can **transfer with feed**, live feeds for certain species and life stages
• **Host carrier**: without expression of disease or mortality; thus, subclinical carriers present an important risk pathway
• Nets, tanks, waders and gumboots, for instance, can act as **fomites** in the transfer of pathogens – in moist conditions
• **Predators, pests, birds and wild aquatic animals** can play a role in the mechanical or vector transmission of pathogens
• **Movement of live aquatic organisms** for trade and other purposes creates important pathways of spread for pathogens.

Know your contamination pathways
• Health certificate guarantees disease status pertaining to listed pathogens/diseases, species, & the procedures that have been followed.

• Higher confidence is achieved where guarantees are based on strict biosecurity, surveillance and testing as applied in the salmonid and shrimp industries.

• In countries where national surveillance data on diseases of aquatic organisms, disease guarantees may be given at compartment level.

• Guarantees based on some form of quarantine combined with visual inspection for clinical signs of illness and mortality, as is still practice for much of the international trade in ornamental fish, are relatively ineffective.

• Suitable husbandry and attention to welfare: essential to maintaining good health and to avoid environments in which microbial pathogens flourish.

• START WITH CLEAN SEED
**STRESS:** inability to adjust to these, may compromise health and resistance to pathogens; negatively affects both the non-specific and specific immune systems and results in a higher susceptibility to disease.

**Sources of stress:** suboptimal environmental conditions: insufficient DO, high stocking densities, suboptimal water temperature, inadequate waste removal or biological filtration, excessive light intensity, wide size variation in the cultured animals, etc.

**Good sanitation:** simple husbandry measures: disinfection of nets and equipment, cleaning of tanks, removal of biofilms, fallowing of cages and sun drying of ponds.

Where boats and vehicles and other equipment are used, particularly for live transfers of aquatic animals, **regular disinfection** when moving between aquaculture sites.

**Collection, transport and disposal of daily mortalities** be made in leak proof containers that are regularly removed from production sites and the rapid disposal through burning, or burial in landfills.
• **Leaching** from medicated pellets from *uneaten food*, and through **excretion from treated animals**, results in contamination of the environment.

• **Legislation**: use of antimicrobials, dispensing of medicines. correct prescription procedures are followed based on an established client-patient-veterinarian relationship.

• **Treatment**: correct diagnosis taking into account the, often, multifactorial causes of microbial disease outbreaks.

• **Medicated feed**: timing of treatment is important. Early intervention, when affected population is still feeding, may save a significant number of animals. Treatment late in a disease outbreak, when many animals are sick and no longer feeding, may achieve poor results.

• **Vaccination**: successful alternative to antimicrobials in reducing the impact of antimicrobial diseases in some cultured species.

• **Regular health monitoring** through disease surveillance and good records of mortality rates and production trends allows early recognition of microbial disease outbreaks and initiation of effective treatment strategies.
• Process by which **management procedures** can be evaluated; **auditable process** from farm to national level - an essential requirement by many countries when live aquatic animals or their gametes are traded internationally.

• **Standard operating procedures (SOPs):** risk assessment: identification and prioritization of hazards (**what can go wrong**), assess the risk (**how likely is to go wrong**), define the pathways of entry to a population of aquatic animals and the relevant control measures (**critical control point evaluation and remediation**).

• **Disease surveillance and monitoring** of existing health problems, contingency actions and eradication measures where the possibility exists of a disease-free status being reinstated.

• **Biosecurity SOPs:** generic guidance need to fit local conditions

• **Emergency:** rapid response plan, who to contact, which samples and data to collect, reporting to Competent Authority (CA) if a disease outbreak is associated with a listed disease, and when to notify neighbouring farms.
DG Bulletin No. 2006/32 “FAO Reference Centres”, a call for expression of interest was released in April 2017. 26 institutional applicants; 13 candidate institutions passed the evaluation process and four of the 13 are selected as candidate centers, currently under further evaluation.

**FAO Candidate Centers for Aquaculture Biosecurity and AMR**

- provide technical services/advice which the Organization is not equipped to provide itself.
- 4 years designation
- undertake with FAO joint activities to promote and support future research and training
- conduct joint resource mobilization
- privilege access to FAO’s policy, technical resources, knowledge and experience

Webinar planned for November
<table>
<thead>
<tr>
<th>Understanding the threat (Smith, 2017)</th>
<th>Avoiding the threat</th>
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<tbody>
<tr>
<td>Which bacterial pathogens for which species?</td>
<td>If we wish to avoid re-entering the pre-antibiotic age we must learn how to use antibiotics wisely</td>
</tr>
<tr>
<td>How are these bacterial diseases being prevented/managed? Good husbandry, vaccines, antibiotics, other alternatives?</td>
<td>Although we have very little idea about how much we use in aquaculture we do know that we must use less.</td>
</tr>
<tr>
<td>Source attribution of AMR in aquaculture associated bacteria is very complex and caution needs to be exercised in interpretation of data. Mere detection of AMR in aquaculture systems does not imply misuse of antimicrobials in aquaculture.</td>
<td>We need antibiotics but we must learn to use antibiotics only when that use is necessary, prudent and rational.</td>
</tr>
<tr>
<td>Is there a direct link between the resistance profile and AMU. AMR may be naturally present in the aquatic environment or derived from AMU in other sectors or derived from AMU in aquaculture</td>
<td>When we use antibiotics, we must learn the most effective and efficient method to administer them.</td>
</tr>
</tbody>
</table>
Key message: Important role of farmers

Disease costs are too high for small-scale sector to survive

Understanding their needs and expectations

Getting them involved and utilise their indigenous knowledge

How do you deal with thousands of small-scale aquaculture producers?

Effective technologies and strategies which are accessible and affordable to the resource-poor small-scale sector

Making them aware of the risks and helping them manage the risks at farm level

Provide feedback and updates
Key message: Better understanding, coordinated and integrated actions

- Aquaculture biosecurity and AMR may be complex & are driven by many interconnected factors.
- Single, isolated interventions have limited impact.
- Greater innovation, research and investment are required in surveillance, MRLs, new antimicrobials, vaccines for low value species, other alternatives to antimicrobials and diagnostic tools.
- Aquaculture producing countries need to develop the aquaculture component, integrate to country NAPs.
- We need to continue to better understand AMR in aquaculture and its coordinated integration into One Health.
AMR and Aquaculture Biosecurity: priority for the work of FAO, COFI/SCA and a number of Priority Programme Areas such as Blue Transformation, One Health, Safe Food, the FAO Action Plan on AMR (2021-2025) and AMR Tripartite (FAO, OIE, WHO) + UNEP