The promise of aquaculture and the challenge of antimicrobial use

This article is published in two parts. Part 1 identifies the promise of aquaculture and the challenge of antimicrobial use (please see the OIE Bulletin 2-2012, 3-9) and Part 2 discusses the measures that are being taken to manage the challenge of antimicrobial use.

Managing the challenge of antimicrobial use in aquaculture

There is a great need to further the training and deployment of veterinarians and aquatic animal health professionals. Clinical pharmacology related to poikilothermic animals is only one of the additional areas of study needed; among the others are: the diagnosis and treatment-related aspects of population medicine (epidemiology, health/disease dynamics, nutrition, clinical microbiology) and an enhanced knowledge of and ability to manage complex animal husbandry systems, such as coastal net pens, open ocean systems, land-based ponds, and raceway and recirculating systems, including an understanding of their environmental impact.

More specifically, with regard to antimicrobial resistance (AMR), there is a need to develop enhanced methods of microbiological culture and antimicrobial susceptibility and testing (AST). Antimicrobial resistance surveillance and monitoring programmes should be developed for aquatic animals and products of aquatic animal origin. The recent adoption of Chapter 6.5., ‘Development and harmonisation of national antimicrobial resistance surveillance and monitoring programmes for aquatic animals’, into the World Organisation of animal Health (OIE) Aquatic Animal Health Code (Aquatic Code) provides particular guidance on this topic. These programmes should be integrated with existing programmes for terrestrial animals and linked with programmes for human disease.

The regulatory infrastructure should be strengthened by promulgating veterinary legislation where it does not yet exist, advancing risk assessment methodologies, and applying effective risk management controls. Non-regulatory controls, such as good aquacultural practices (e.g. the Joint Institute for Food Safety and Applied Nutrition’s Good Aquacultural Practices Manual: http://jifsan.umd.edu/training/gaqps_manual.php) and standards on responsible use, such as those in the OIE Aquatic Code, as well as guidelines published by the Food and Agriculture Organization of the United Nations (FAO) (ftp://ftp.fao.org/docrep/fao/009/a0282e/a0282e00.pdf), AVMA (Judicious Use of Antimicrobials for Treatment of Aquatic Animals by Veterinarians) and others, are needed to provide an acceptable framework for administering antimicrobials to aquatic species. More comprehensive data are required as a sound basis for risk analysis, alongside advanced methodologies that take into account the diversity of aquatic culture systems.
Strengthening national Veterinary Services and Aquatic Animal Health Services

For accurate diagnosis and treatment of infections in aquatic species, access to veterinarians and aquatic animal health professionals is essential. Moreover, to protect public health and ensure animal health, as well as to meet their obligations for international trade in food, countries must have adequate national services, both Veterinary Services (VS) and Aquatic Animal Health Services (AAHS), if these are separate from VS. Through the OIE Evaluation of the Performance of Veterinary Services (PVS) Pathway programme, OIE Member Countries can request an evaluation of their VS and AAHS infrastructure against the OIE standards for quality. After an initial evaluation, countries may request a PVS Gap Analysis, as a way to assign national priorities and provisional budgets for necessary investment. The PVS Evaluation and Gap Analysis form the basis for a comprehensive national plan to strengthen VS/AAHS with the aims of developing:

– human, physical and financial resources, to attract more resources and retain professionals with technical and leadership skills
– the technical authority and capability to address new and current issues, including the prevention and control of biological disasters, based on scientific principles
– sustained interaction with stakeholders to carry out relevant joint programmes and services in a sustainable manner, and
– the ability to access markets through compliance with standards and the implementation of new disciplines, such as harmonisation, equivalence and zoning.

The national plan will typically contain recommendations for promulgating veterinary legislation, leveraging public/private partnerships, improving veterinary education and governance and establishing or enhancing laboratory services.

Modernising veterinary legislation

Veterinary legislation is an essential element of the national infrastructure that enables VS/AAHS to efficiently carry out their key functions, including epidemiosurveillance; early detection and reporting of diseases, including zoonoses; rapid response to and prevention and control of animal health emergencies; animal production food safety; animal welfare and the certification of animals and animal products for export. Unfortunately, veterinary legislation in many countries is outdated and inadequate to deal with the challenges faced by VS/AAHS today and in the future. For this reason, the OIE has made provision for Member Countries to request assistance with modernising their veterinary legislation within the PVS framework.
The authorisation and use of veterinary medicines, including those to treat aquatic species, also require an adequate legal framework. Pre-market evaluation and authorisation of veterinary medicines can include assessments of effectiveness; animal safety; human food safety (for food producing species); product chemistry, manufacturing and controls; and environmental impact. Importantly, pre-market authorisation includes a review of appropriate labelling, including the need for veterinary supervision of certain products. Post-market surveillance of adverse reactions, including a lack of effectiveness potentially caused by antimicrobial resistance, may also be a requirement of legislation. In some cases, legislation can also contribute to the establishment of surveillance and monitoring systems for evaluating the incidence of resistant micro-organisms and examining trends in the quantities of antimicrobials used. Trends in the incidence of resistant micro-organisms and the quantities of antimicrobials used may be useful in evaluating possible associations. The recently adopted Aquatic Code, Chapter 6.4., `Monitoring of the quantities and usage patterns of antimicrobial agents in aquatic species`, provides guidance on this topic.

Addressing the lack of approved drugs

In order to minimise inappropriate use and misuse of antimicrobials and to provide safe and effective therapies, an effective pre-market authorisation process is required. This process requires the generation of data to support the effectiveness of veterinary medicines, as well as their safety for humans and animals, and to gauge their environmental impact. In addition, marketed products need data on manufacturing chemistry and controls to demonstrate their purity, safety, potency and stability. Generating these data in multiple species, at various dosages, in different water chemistries, requires a significant investment by the drug sponsor. Often, specific data are needed to support the authorisation of drugs for disease in a particular species under various conditions of use. Aquatic animal drug sponsors are simultaneously challenged to commit resources to fractionated industry segments. To address the issue of data generation and the need for approved drugs for aquatic species in both public (e.g. conservation and management of important species) and private sectors (e.g. commercial culture), a variety of approaches have been launched. Public/private partnerships have been successful in generating data and analytical methods that support the public sector mission, while also making this information available for use by the private sector, to support the licensing of products that might not otherwise have sufficient commercial interest. In addition, some countries have adopted Minor Use Minor Species (MUMS) legislation to make more medications legally available to
veterinarians and animal owners to treat minor animal species and uncommon diseases in the major animal species. Such legislation can facilitate innovative ways to bring products for small populations to market and is designed to help pharmaceutical companies overcome the financial roadblocks they face in providing limited-demand animal drugs.

Using risk analysis as a tool to address the risks of antimicrobial resistance in aquaculture

The principles of risk analysis, risk assessment, risk management and risk communication are applicable to address the risks of AMR in aquaculture, using a similar approach to that used in other food production sectors. Multilateral organisations and national and regional authorities have invested considerable effort over the past ten to 15 years towards the goal of improving risk assessment and the management of antimicrobial use in aquaculture.

Beginning in 1997, with the World Health Organization (WHO) meeting on the medical impact of the use of antimicrobials in food animals, a series of meetings and expert consultations were held by WHO/OIE/FAO (www.who.int/foodborne_disease/resistance/meetings/en/), resulting in:

– the publication of global principles for the containment of antimicrobial resistance in food animals (2000),
– the development and refinement of lists of critically important antimicrobials for human and veterinary medicine (2005–2007),

In 2006, an important FAO/WHO/OIE consultation focused solely on the issue of antimicrobial use in aquaculture (Joint FAO/OIE/WHO Expert Consultation on Antimicrobial Use in Aquaculture and Antimicrobial Resistance, Seoul, Republic of Korea, 13-16 June, 2006). Outcomes of that meeting included a better understanding of the diversity of aquaculture; the first attempts to apply the principles of risk analysis to AMR in aquaculture; and the identification of knowledge gaps with respect to AST methods and the complexity of exposure pathways for horizontal gene transfer.

Meanwhile, within the Codex framework, food standards, codes of practice and guidelines were also evolving to address the risks of foodborne antimicrobial resistance, including within aquaculture products. Building on several publications, including Food safety risk analysis, a guide for national food safety authorities (FAO #87-2005); Code of practice to minimise and contain antimicrobial resistance (CAC/RCP 61-2005); Principles and guidelines for the conduct of microbiological risk assessment (CAC/GL 30-1999); and Principles and guidelines for the conduct of microbiological risk
management (CAC/GL 63-2007), the Codex guideline, *Risk analysis for foodborne antimicrobial resistance* (CAC/GL 77), was adopted in 2011. This document sets out principles for conducting risk analysis for foodborne antimicrobial resistance, including in aquaculture products.

Since 2003, the OIE has adopted specific chapters on AMR into the *Terrestrial Animal Health Code*, including one on risk assessment, and these continue to be updated and revised to reflect the latest scientific knowledge. In 2010, the OIE requested the *ad hoc* Expert Group on the Responsible Use of Antimicrobials in Aquaculture to draft complementary advice on aquatic animals, for inclusion in the *Aquatic Code*. As of 2012, four chapters have been adopted, i.e. Chapter 6.2., ‘Introduction to the recommendations for controlling antimicrobial resistance’; Chapter 6.3., ‘Principles for responsible and prudent use of antimicrobial agents in aquatic animals’; Chapter 6.4., ‘Monitoring of the quantities and usage patterns of antimicrobial agents used in aquatic animals’ and Chapter 6.5., ‘Development and harmonisation of national antimicrobial resistance surveillance and monitoring programmes for aquatic animals’. The guidance provided in these chapters is essential for the creation of a framework to conduct risk analysis. In order to conduct meaningful risk assessment and to evaluate potential risk management options and monitor their effectiveness, systems must be established and supported to generate data and information. Integrating these systems with analogous systems for collecting and analysing human and animal data will be important in understanding possible associations between antimicrobial use and AMR.

**Conclusions**

Clearly, it is necessary to address the challenges associated with antimicrobial use in aquatic animals in order to fulfil the promise of aquaculture.

The future of aquaculture remains bright and the promise of a blue revolution in this century to match the green revolution of the past century is still within the realms of possibility. A recently published FAO expert paper, entitled: ‘How to Feed the World in 2050’ (www.fao.org/fileadmin/templates/wsfs/docs/expert_paper/How_to_Feed_the_World_in_2050.pdf), makes a compelling case for the need to greatly increase food production in the not-too-distant future. Aquaculture will almost certainly make a significant contribution towards meeting these demands. As with any new food production sector there will be challenges, but if the world demand for high-quality, sustainable animal protein is to be met, these challenges, including AMR, must be addressed. We are well on our way towards defining the gaps in our knowledge that must be filled to reap the benefits of aquaculture. As
these gaps are rectified, we will be able to use our most powerful tools (e.g. bioinformatics, genomic research, sophisticated computer modelling) to further monitor the selection and dissemination of resistant micro-organisms and understand the impact of antimicrobial use. It will be important for the private sector to continue to support growth in aquaculture (e.g. through approved drugs, new culture systems and advanced nutrition). It will be crucial for national and regional governmental authorities, with the help of the OIE and other international organisations, to develop frameworks that enhance food safety and facilitate the trade of food products derived from aquatic species. It will also be important for professional educational bodies to take steps to enhance the knowledge and expertise of veterinarians and aquatic health professionals, and for professional organisations to support the continued development of their members working in the aquatic arena. With these elements in place, we have the best possible chance to address the challenge of antimicrobial use and fulfil the promise of aquaculture.

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