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Short Communication

# Antibiotic Resistance in Fish Farming Environments: A Global Concern

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## Antibiotic Resistance in Fish Farming

The occurrence and distribution of antibiotic resistance (AR) phenomena in areas designed for fish Farming has exponentially increased in the last decades. AR bacteria have become a global concern due to the massive use or misuse of antibiotics to prevent possible diseases and overcome major production problems, as confirmed by several research reports (Hansen, P.K., Lunestad, B.T., Samuelsen, O.B. 1993; Smith, P., Hiney, M.P., Samuelsen, O.B. 1994; Alderman, D.J., Hastings, T.S. 1998; Cabello, F.C. 2006; Heuer, et al. 2009; Millanao, et al. 2011; Park, Y.H., Hwang, S.Y., Hong, M.K., Kwon, K.H. 2012; Romero, J., Feijoó, C.G., Navarrete, P. 2012; Cabello, et al. 2013). As a consequence of the selective pressure exerted by antibiotics, ARB has been developed and multi-drug resistant bacteria (MDR) have become difficult to be controlled and eradicated. Their spread is expected to increase and is recognized to represent one of the most serious threats to public health in this century. Compared to the past, in salmonid farming in Europe and America, an effective range of vaccines has been developed, which have allowed decreasing the use of antimicrobial agents for most of the bacterial diseases (Alderman, D.J., Hastings, T.S. 1998). In addition, the husbandry methods and diagnostic techniques have been improved and this has resulted in a more effective control of bacterial pathogens and reduced impacts of fish diseases. However, for some bacterial diseases, no vaccines are available yet (Sommerset, I., Krossøy, B., Biering, E., Frost, P. 2005; Adams, A., Thompson, K.D. 2011) and antimicrobials are still used as a prophylactic measure.

This short note aims at drawing a synthesis of the AR occurrence in aquaculture field and of the possible causes for its spread, suggesting the related legislative measures and the possible solutions to this emerging problem, which has been recognized as a research priority issue by the European Community.

Since the first case studies (Hansen, P.K., Lunestad, B.T., Samuelsen, O.B. 1993; Smith, P., Hiney, M.P., Samuelsen, O.B. 1994; Alderman, D.J., Hastings, T.S. 1998), several reports have documented the occurrence and spread of ARB in both marine and freshwater fish farms (Schmidt, A.S., Bruun Morten, S., Dalsgaard, I., Pedersen, K., Larsen, J.L. 2000; Miranda, C.D., Zemelman, R. 2002a; Chelossi, et al. 2003; Akinbowale, O.L., Peng, H., Barton, M.D. 2006; Laganà, P., Caruso, G., Minutoli, E., Zaccone, R., Delia, S. 2011). Most frequently, AR has been reported against oxytetracycline (DePaola, A., Peller, J.T., Rodrick, G.E. 1995; Miranda, C.D., Zemelman, R. 2002b), tetracycline (Akinbowale, O.L., Peng, H., Barton, M.D. 2007; Miranda, C.D., Kehrenberg, C., Ulep, C., Schwarz, S., Roberts, M.C. 2003), ampicillin (Su, et al. 2011) florfenicol (Miranda, C.D., Rojas, R. 2007). On the contrary, bacteria resistant to gentamicin, kanamycin, flumequine and enrofloxacin have been reported to account for a low percentage of the total of the isolates (Miranda, C.D., Zemelman, R. 2002a).

Fish feed have been claimed to be a source of antimicrobial-resistant bacteria (Kerry, et al. 1995; Economou, V., Gousia, P. 2015). Concerning the mechanisms of AR, two main pathways have been suggested (Romero, J., Feijoó, C.G., Navarrete, P. 2012): a) inherent or intrinsic resistance, which occurs when a bacterial species is not normally susceptible to an antibacterial agent, due to the inability of this agent to reach its target site inside the cell, or a lack of affinity between the antibacterial and its target site, or b) acquired resistance, when the bacterial species is normally susceptible to a particular drug, but some strains are resistant and proliferate under the selective pressure induced by the use of that agent. AR genes can be transferred between bacteria by transformation; transduction or conjugation processes that involve lateral DNA transfer (Romero, J., Feijoó, C.G., Navarrete, P. 2012). Therefore, bacterial AR is a natural defence mechanism realized through genetic modifications triggered to survive to the drug action and in many conditions, mechanisms of horizontal gene transfer have been reported to be responsible for the spread and dissemination of the genetic material bearing AR among different bacterial species (Miranda, C.D., Tello, A., Keen, P.L. 2013). Even in some aquaculture systems of Pakistan and Tanzania where antibiotics were not previously used (Shah, S.Q.A., Colquhoun, D.J., Nikuli, H.L., Sørum, H. 2012); explained the occurrence of AR against various antimicrobials hypothesizing that a pool of resistance genes derived from integrated fish farming practices based on the use of domestic farm and poultry waste along with antibiotic residues from animal husbandry.

The public health hazards related to antimicrobial use in fish farming include, on one hand, the development and spread of AR bacteria and resistance genes, and on the other, the presence of antimicrobial residues both in the environment and in aquaculture products (Romero, J., Feijoó, C.G., Navarrete, P. 2012). Since animals and animal waste are a potential reservoir of multi resistance genes that can be transmitted directly or indirectly to humans through contact and food consumption, this can represent a risk to public health. However, the opinions on the possible risks of transfer of such resistances to human consumers are controversial (Alderman, D.J., Hastings, T.S. 1998; Economou, V., Gousia, P. 2015; Igbinosa, E.O. 2016). Antibiotic-resistant bacteria that persist in sediments and farm environments can act as sources of antibiotic-resistance genes for fish pathogens in the vicinity of the farms.

With respect to the legislative issues of the AR in fish farming, this issue has been recognized as a global concern by the Council and the European Parliament, as well as by the EU Commission. The Regulation (EC) No 470/2009 established the antibiotic maximum residue limits (MRL) in foodstuff of animal origin, taking into account the toxicological risks and the pharmacological effects of residues. The recently launched research programme Horizon 2020, in the framework of the Societal Challenge 3.2 (Food Security, Sustainable Agriculture and Forestry, Marine, Maritime and Inland Water Research and the Bioeconomy), promotes the reduction of antibiotics in animal farming and the setup of measures to prevent their spread, to increase agriculture environmental sustainability. This underlines the relevance of AR in fish farming as a problem with significant scientific, social and economic impacts.

In 2011, a 5-year Action Plan was launched to address the growing risks posed by AR based on a holistic approach; a prudent use of antimicrobial in veterinary medicine was recommended.

To comply with this Action, in 2015 specific guidelines have been issued (2015/C 299/04, Commission Notice-Guidelines for the prudent use of antimicrobials in veterinary medicine), with the aim of limiting AR bacteria originated from livestock animals. Among the actions recommended to prevent and reduce the use of antimicrobials in aquaculture, it has been underlined to encourage the use of vaccines, when possible; to implement specific biosecurity measures and to develop specific disease surveillance programmes to prevent or reduce possible disease outbreaks; to develop production systems optimal with respect to water quality, oxygen levels and able to warrant the welfare of the reared animals.

Compared to the studies available until now on the antibiotic use in aquaculture or other farm environments and the presence of AR, relatively few studies focused on the possible solutions to this problem. To implement the appropriate control strategies, a clear evidence of the link between abuse of antibiotics in aquaculture, antibiotic resistance in bacterial pathogens and antibiotic residues is needed. In order to contain and manage the emergence of AR, several solutions can be suggested, that aim at the development of sustainable aquaculture practices, such as those including the use of probiotics, essential oils to increase fish immune status of fish (Romero, J., Feijoó, C.G., Navarrete, P. 2012; Sihag, R.C., Sharma, P. 2012), as well as the adoption of measures able to warrant the fast abatement of antimicrobial residues in animal wastes (The Review on Antimicrobial resistance 2015). Particularly, the use of probiotics to promote health maintenance and disease prevention has recently gained an increasing interest as an alternative to antibiotics (Martinez, C.P., Ibanez, A.L., Monroy Hermosillo, O.A., Ramirez Saad, H.C. 2012; Ram, C.S., Parvati, S. 2012). Supplementation with pro- and prebiotics in fish nutrition is increasing in parallel with increasing demand by consumers and with the need for environmentally friendly aquaculture practices (Denev, S., Staykov, Y., Moutafchieva, R., Beev, G. 2009). The beneficial effects of probiotics in fish and shellfish culture - improved growth performance, activity of gastrointestinal microbiota and feed utilization, enhanced immunity and disease resistance - have recently been reviewed (De, et al. 2014). Most probiotics proposed as biological control agents in aquaculture belong to the lactic-acid bacteria (LAB), the genus *Bacillus*, or the genera *Pseudomonas* and *Burkholderia* (Ringo, E., Gatesoupe, F.J. 1998; Balcazar, et al. 2008; Kesarcodi-Watson, A., Kaspar, H., Lategan, M.J., Gibson, L. 2008).

Another possible solution to chemotherapies in aquaculture is related to the use of vegetable extracts. Herbal extracts from plants or algae are known to contain natural compounds, such as phenolic compounds, polysaccharides, proteoglycans and flavonoids which are able to stimulate the fish immune system and therefore may play a major role in the prevention or control of infectious microbes (Reverter, M., Bontemps, N., Lecchini, D., Banaigs, B., Sasal, P. 2014).These are recognized as eco-friendly alternatives for therapeutic and prophylactic purposes in health management of aquatic animals, which combine sustainable production systems with high quality of seafood products; nevertheless, further studies are needed to assess any potential impact of these substances on the host microbiota and on the environment.

About the treatment of aquaculture effluents, antibiotic residues should be removed before being released to the environment. Physical, chemical, and biological methods including adsorption, biodegradation, disinfection, membrane separation, hydrolysis, photolysis, and volatilization have been applied in aquaculture systems to remove antibiotics (Chuah, L.O., Effarizah, M.E., Goni, A.M., Rusul, G. 2016). Tetracyclines are removed mainly by adsorption onto the biomass flocs; beta-lactams by hydrolysis reactions driven by bacteria or physical chemical processes, while removal of erythromycin and ciprofloxacin by biodegradation is difficult. Advanced oxidation processes have been found to be cost-effective mechanisms for the abatement and removal of flumequine from aqueous systems, as conventional processes in wastewater treatment plants fail to remove this antibiotic (Feng, et al. 2016).

In synthesis, on the basis of the experimental evidences proving the spread of AR, the best way to solve this problem is to avoid abuse antibiotic use in aquaculture. A holistic approach to the use of antibiotics in fish farming is suggested, which relies on reducing the need for antibiotics through prevention (i.e. vaccines), nutrition, and better management of rearing sites.

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