

## ANTIMICROBIAL RESISTANCE AND AQUACULTURE

The spread of antimicrobial resistance (AMR) has been classified by the World Health Organization (WHO) as one of the major threats facing the human population this century. It could become the leading cause of death, exceeding cancer, and result in as many as 10 million mostly premature deaths a year by 2050. The development of AMR limits the effectiveness of antibiotic treatments of bacterial infections in humans and species produced in aquaculture.

AMR occurs when a microorganism develops resistance to antimicrobial agents. It is a natural process, but residues of human overuse and misuse of antibiotics have increased the selection pressure that leads to AMR. Resistance can be acquired through genetic mutation and horizontal gene transfer among microbial populations.

Globally around 70 percent of antibiotics are used in animal husbandry and 30 percent in human medicine. Up to 80 percent of consumed antibiotics are not metabolized and thus excreted. These sub-lethal levels of antimicrobial residues then enter wastewater treatment systems or released directly to soil or water and interact with environmental bacteria, leading to selection of AMR strains. Humans can be exposed to AMR bacteria through food consumption, drinking water and direct environmental contact.

Wastewater treatment plants are hotspots for horizontal gene transfer due to high bacterial density and nutrient richness. AMR bacteria can be found in water and sediment near discharges from industrial and municipal wastewater facilities as well as fish and shrimp farms. An astounding 90 percent of bacteria in seawater are resistant to at least one antibiotic. The genes that confer resistance to antimicrobials can be found in clinically important fish and human pathogens and environmental bacteria in water and soil.

The rapid growth in aquaculture has been accompanied by production intensification, resulting in an increased risk of disease outbreaks that are often treated with antimicrobials. Up to 75 percent of antibiotics used in aquaculture may be released to the surrounding environment. The application of antimicrobials affects targeted pathogens as well as a wide variety of environmental bacteria, resulting in selection of AMR strains that increase the risk of horizontal gene transfer to potential human pathogens.

One noteworthy example of this was demonstrated in Chile, where genes from quinolone-resistant aquatic bacteria were isolated from a salmon farming area with a history of heavy quinolone usage. Quinolone resistance genes were subsequently isolated from *E. coli* that caused urinary tract infections in people living in Puerto Montt, near the salmon farming area, clearly demonstrating horizontal gene transfer.

AMR genes can appear on fish farms even when antibiotics are not used. Jing Wang of Dalian University in China published a paper in 2017 called "Fishmeal Application Induces Antibiotic Resistance Gene Propagation in Mariculture Sediment." The authors tested five commercially available fishmeals in China and found 132 AMR genes, ranging from 8 in fishmeal from Russia to 95 in fishmeal from China. In lab studies, these resistance genes were also isolated

from sediment bacteria, indicating horizontal transfer from bacteria in fishmeal to sediment bacteria. The authors suggested that efforts should be made to remove AMR genes from fishmeal before using in aquafeeds.

At present and as a practical matter, there are very few alternatives to antibiotics to treat diseases in intensive aquaculture. In general, a preventative approach is essential to reduce the use of antimicrobials. Methods to increase the resistance of fish hosts to disease include using nutritionally optimized feed and good feeding practices, minimizing stress, stimulating the immune system with vaccines and immunostimulants, and genetic selection for disease resistance. To maintain a good culture environment, BMPs, good hygiene with quarantine and disinfection, water quality management and the use of probiotics and synbiotics offer promise. To control pathogens, bacteriophages that infect and kill pathogens, phytochemicals like essential oils, and quorum sensing disruptors or inhibitors are future options.

In the big picture, the overuse of antibiotics in aquaculture, especially prophylactic use, must be stopped. Antibiotics should be used only to treat diagnosed bacterial diseases. A reduction in antibiotic use in aquaculture must become a trend.

Of course, stricter regulations and better enforcement could limit the development of AMR. In general, antibiotic use in developed countries is fairly well regulated. However, in many countries that are major aquaculture producers, regulation and enforcement is weak and inadequate. Food-safety regulations that set maximum residue limits can serve as a powerful disincentive to use antibiotics on aquaculture products that are exported to developed country markets with strong regulatory systems. Aquaculture ecolabeling schemes can also limit the spread of AMR genes through traceability systems.

AMR has been described as the "quintessential" One Health issue. The One Health approach works towards "optimal health for people, animals and our environment." The One Health approach is a useful framework that recognizes the interconnectedness of aquaculture production and human health. There are numerous questions about AMR and aquaculture that require a concerted and coordinated research effort. Specifically, the link between antibiotic use in aquaculture and AMR pathogenic bacteria in humans needs further elucidation.

The Collier FAIRR (Farm Animal Investment Risk and Return) Protein Producer Index provides a comprehensive assessment of how the world's 60 largest publicly-listed meat and fish producers are managing critical sustainability risks. The companies were evaluated on the basis of nine sustainability risk factors, including antibiotic use. The good news is that four of the top five companies ranked as lowest risk are salmon producers, led by Marine Harvest, which was the top scoring company overall. However, the bad news is that antibiotic mismanagement is the most poorly addressed risk. There is clearly a long way to go overall, but salmon farming, at least as practiced in Norway, can show the way forward to manage that risk.

— *John A. Hargreaves, Editor-in-Chief*