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BACKGROUND BRIEF 4
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Antibiotics in Aquaculture

The complexity and gravity of current trajectories of antimicrobial resistance (AMR) due to antibiotic use in food producing species, including aquaculture, call for the immediate mass mobilization of society. The problem involves a complex and interconnected system of pressures, AMR pathways and risks.

Escalating global threat

Antimicrobial resistance (AMR) is one of the greatest human health and sustainability challenges of the 21st century[1]. Excessive use of antibiotics for treatment of people and farmed animals has altered natural bacterial communities and led to the increase in AMR. Acquired AMR in humans renders antibiotics essential for treating infections and carrying out common surgical procedures inefficient. Currently, approximately 700,000 annual deaths are attributable to infections by drug-resistant pathogens and, if unchecked, this may increase to 10 million by 2050[2].

The reliance on antibiotics in animal food production is high. In addition to posing direct and indirect threats to human health through development of AMR, it also threatens food systems and wildlife (Figure 1) due to leakage of antibiotics into the broader environment. More than half of the seafood consumed globally originates from aquaculture, and the sector makes an important contribution to human nutrition. Use of antibiotics by the aquaculture sector is substantial but there is a lack of a comprehensive overview of use. This limits our understanding about the risks of AMR development and factors behind antibiotic use.

Glossary

Antibiotics - a type of antimicrobial substance active against bacteria.

Antimicrobials - an agent that kills microorganisms or stops their growth.

Antimicrobial resistance (AMR) - ability of a microorganism to resist the effects of medication.

Antibiotic resistance (AR or ABR) - a subset of AMR, as it applies only to bacteria becoming resistant to antibiotics

Antimicrobial/antibiotic residue – a remains of a compoud or its intermediate metabolic products.

Prophylactic - use of e.g. antibiotics to prevent emergence of a bacterial infection

Horizontal gene transfer - movement of genetic material between unicellular and/or multicellular organisms other than DNA transfer in reproduction.

Increased use of antibiotics in aquaculture production

Overall, antibiotic use in the livestock sector is increasing and estimates of total use range from around 63,000 tons, to over 240,000 tons per year[3]. This is equivalent to consumption in human medicine and is estimated to further increase by 67 percent from 2010 to 2030. Recent increases in aquaculture production have, similarly to agriculture, mainly been achieved through intensification of existing farming systems (and increased farm densities), resulting in higher risks of disease outbreaks. This has subsequently led to increased use of antibiotics that now are commonly used, sometimes excessively and/or ineffectively, in a wide range of aquaculture systems and countries[4,5]. Misuse is usually associated with production systems characterized by factors such as high stocking densities, poor hygiene, and insufficient fish health control and/or access to proper farming technologies[11]. Antibiotic-resistant bacteria accumulate in water, sediments, and wild animals in and around farms, which poses a risk to effective treatment of infections in both animals and humans (Figure 1)[5,6].

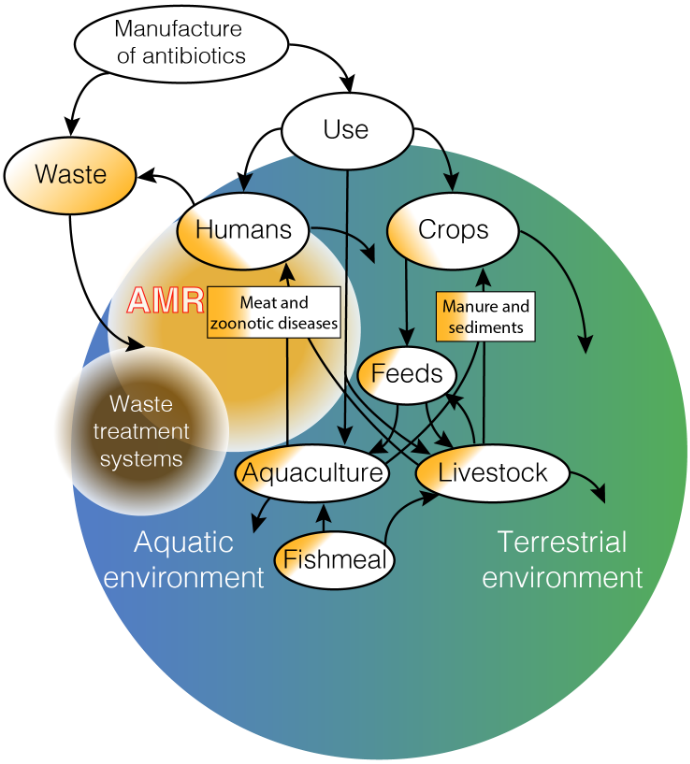


Figure 1: Environmental pathways of antibiotics and their link to AMR.

Different reasons for use

Farmers use antibiotics either for treatment of diseases (especially during the early development phases) as a prophylatic, or as growth stimulant (Figure 2)[7]. Unlike livestock farming, however, growth promotion is limited in aquaculture with non-treatment dominated by prophylaxis[8]. Both growth promotion and prophylaxis are controversial, the former because it does not serve to maintain the health of the animals and both increase the risk of resistant bacteria. Many countries have already banned such use of antibiotics. Bans have been placed, for instance, by the EU in 2006, and in 2017 the US re-labeled 292 veterinary drugs from over-the-counter sale to veterinary prescription status in a scheme to phase out important antibiotics previously used for growth promoting purposes. Field investigations also reveal that information and stricter guidelines have resulted in reduced use as a prophylactic for particular species in particular regions (e.g. pangasius farming in Vietnam[4]).

Antibiotics in the aquatic environment

The challenges for reducing antibiotics are similar for most animal production but there are differences in application, accumulation, and release of antibiotic residues between livestock and aquaculture. Aquaculture is commonly connected with its surrounding environment through water exchange, which implies that released antibiotic residues and resistant bacteria readily spread beyond the farm and that the farm itself is exposed to a more diverse set of pathogens[9]. Antibiotics may impact on aquatic wildlife (i.e. spread of AMR and disruption of host and environmental microbiomes), but this depends on how the farm is connected to the environment. In addition, drugs used in human medicine and agriculture also shape microbiomes in the aquatic environment – i.e. through urban sewage, hospital effluents, and animal farm run-off (Figure 1)[10]. Antibiotic doses in aquaculture can be higher proportionately than those in livestock and residues of antibiotics can remain longer in fish products[2]. About 70-90% of antibiotics given to fish leak into the surrounding environment[2].

Which antibiotics are used in aquaculture?

The type, frequency, and quantity of antibiotics used in aquaculture are determined by a number of underlying factors, including species farmed, farming environment, production technology, farming practices, accessibility to and influence from veterinarian/fish health specialist support, and implementation of food safety regulations in target markets[11]. Antibiotics are also misused due to misdiagnosed diseases. A diverse range of antibiotics are presently used in aquaculture, although stricter legislation has resulted in a move away from the use of medically important antibiotics. However, the same antibiotic classes are used in livestock, aquaculture, and human medicine, which may further increase exposure to a specific antibiotic. The WHO has different categories of antibiotic compounds, varying from important, to highly important, to critically important (including a subgroup of "highest priority" antibiotics that are considered critically important for human medicine). Yet even some of these highest priority antibiotics (e.g. quinolones) are frequently used in aquaculture. Use of 11 banned antimicrobial drugs have been identified in aquaculture production in China and Vietnam, including Chloramphenicol, Ciprofloxacin, Florfenicol, Nitrofurans, and Enrofloxacin[5,6].

The overall picture related to global use is still unclear, but results from recent reviews show that 67 different antibiotic compounds were used in aquaculture in eleven major producing countries between 2008 and 2018[5]. These are related to the main species groups and belong to nine main antibiotic classes (Figure 3). Vietnam and China use the highest number of antibiotics compounds – ranging from 30-40 different compounds. In other countries, such as Japan and Thailand, there has been a reduction in the number of antibiotics used. This is encouraging, but if use is still high from a few antibiotics the problem with resistance development may persist because of co-selection, where one antibiotic confers resistance to antibiotics from other classes.

Evolution of resistance

AMR genes spread among livestock, fish, and humans through effluent water and the use of manure, by-product meals, handling, aerosols, and fishmeal. Recently, 24 unique AMR genes were found in five fishmeal samples from Peruvian anchoveta, codfish from Russia, and mixed sources[12]. All of these samples were

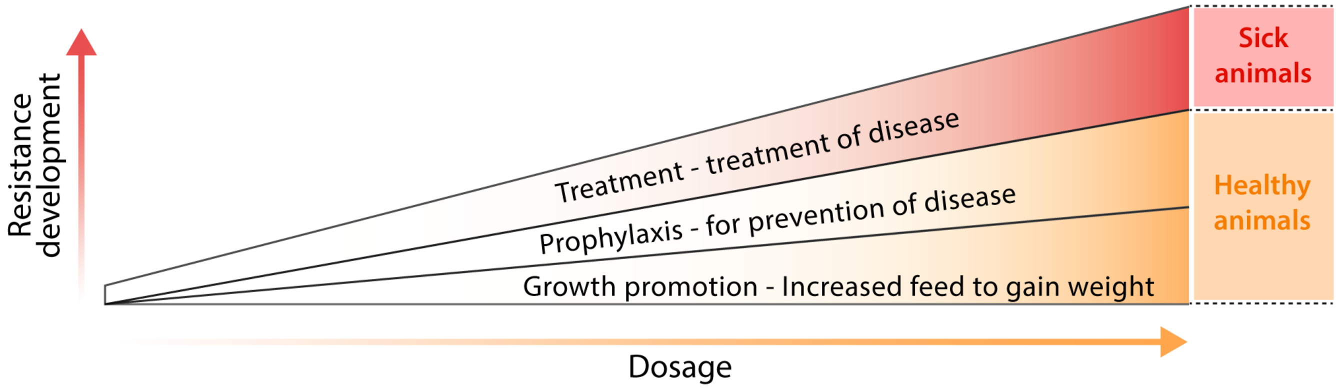


Figure 2: Prophylactic and growth promoting use of antimicrobials results in resistance development, which subsequently undermines therapeutic use on sick animals and can result in much larger dosages overall.

also contaminated with bacteria that have potential to be pathogenic to humans. Elevated frequencies of AMR genes in humans living close to Chilean salmon farms have also been reported. Observations of AMR (e.g. potentiated sulphonamides, penicillins, and phenicols) have been frequently reported across species, but most frequently in shrimp. These types of observations and subsequent media scares (for example CBC News' "Shrimp containing antibiotic-resistant bacteria found in Canadian grocery stores". Mar 15, 2019) are expected to become increasingly frequent as the cost of carrying out such monitoring and observations falls.

Human health impacts from antibiotics used in animal production

AMR infections in animals of highest risk to human health are likely to be zoonotic pathogens transmitted through food, especially Salmonella and Campylobacter. In addition, livestock-associated methicillin-resistant *Staphylococcus aureus* (LA MRSA), extended spectrum beta lactamase *E. coli* (ESBL *E. coli*), and the worrisome carbapenemase producing Enterobacteriaceae are emerging problems throughout the world. Through horizontal gene transfer any form of antibiotic resistance that evolves within aquaculture can be spread to other bacteria within the human health and agricultural systems.

Rapidly increasing use of antibiotics within animal farming sectors is expected to be an important contributor to AMR, as bacteria can easily spread between animals and humans (e.g. MCR-1, MCR-2, MCR-3 genes; livestock associated MRSA in humans and resistant urinary tract infections in humans). The biotechnology revolution has helped to confirm that antibiotic use in animal farming is contributing to the spread of resistance in humans, with multiple examples of spread well-documented using genomic epidemiological methods.

Conclusion and Way forward

The aquaculture industry is highly diverse in terms of both species and systems. A particular governance challenge is posed by the many small-scale farms spread throughout multiple less developed countries, using antibiotics in an uncontrolled manner. Addressing

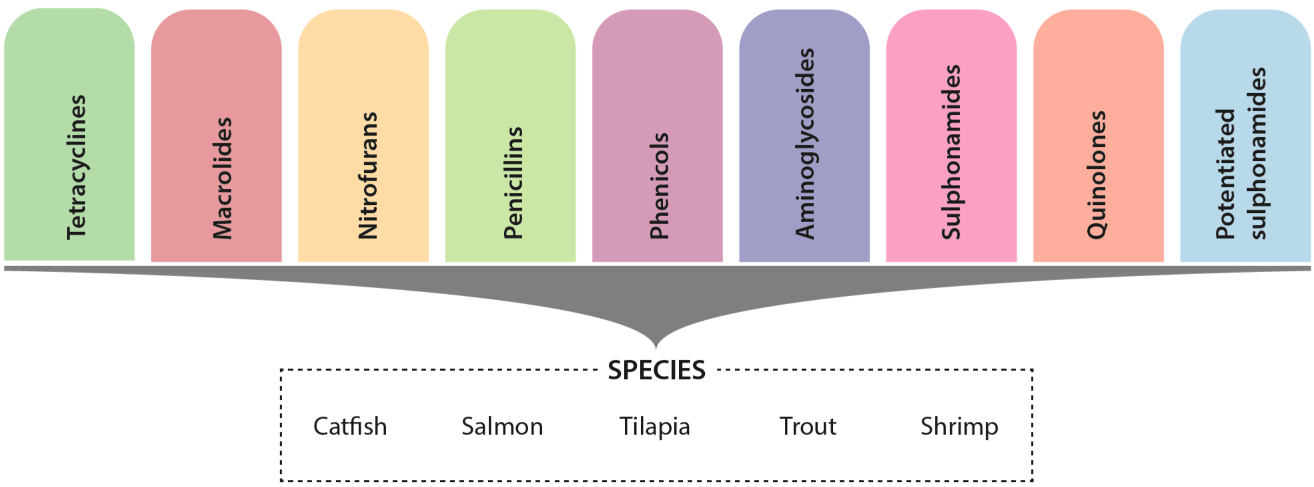


Figure 3. Illustration of the most common antimicrobial drug classes used in farming of dominant aquaculture species.

over-use of antibiotics and emergence of AMR requires awareness raising, improving farm management (practices and monitoring), technology development (e.g. vaccines), and stricter regulation and controls.

Promoting transparency in use of antibiotics

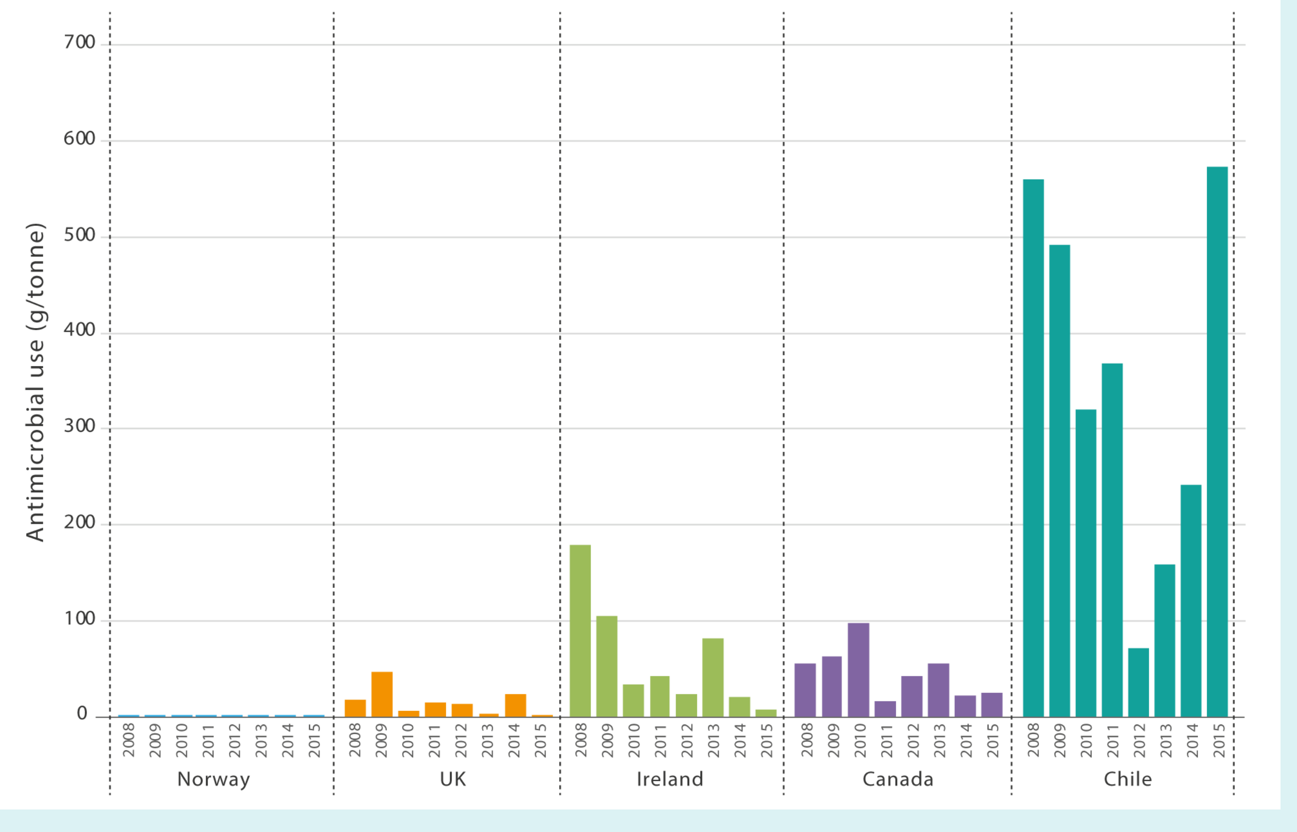
Volumes of antibiotics used are strongly linked to AMR development, but application method and frequency are also of importance. The European Surveillance of Veterinary Antimicrobial Consumption[13] has suggested guidelines for how and when antibiotic use should be recorded for husbandry animals. These data are later made public to help academia, authorities, and sectors tackle excessive use. The Global Salmon Initiative[14] has adopted a similar approach, which has incentivised reduction.

Building recognition for the UN's 'One Health Perspective

'One Health' is an approach to designing and implementing programs, policies, legislation, and research in which multiple sectors communicate and work together to achieve better public health outcomes[1]. Combatting antibiotic resistance is a central focus of this work. Antimicrobial stewardship recognizes that most bacteria are harmless or beneficial for animals, including aquaculture species, and that bacteria susceptible to antibiotics are a non-renewable resource being depleted by antibiotic use[15]. Antimicrobial stewardship in aquaculture therefore seeks to limit antibiotic use to an absolute minimum to protect a critical resource that saves millions of human lives every year and seeks alternative methods for producing quality aquaculture products through a diversity of interventions and innovations in aquaculture production systems.

Box 1: Vaccines

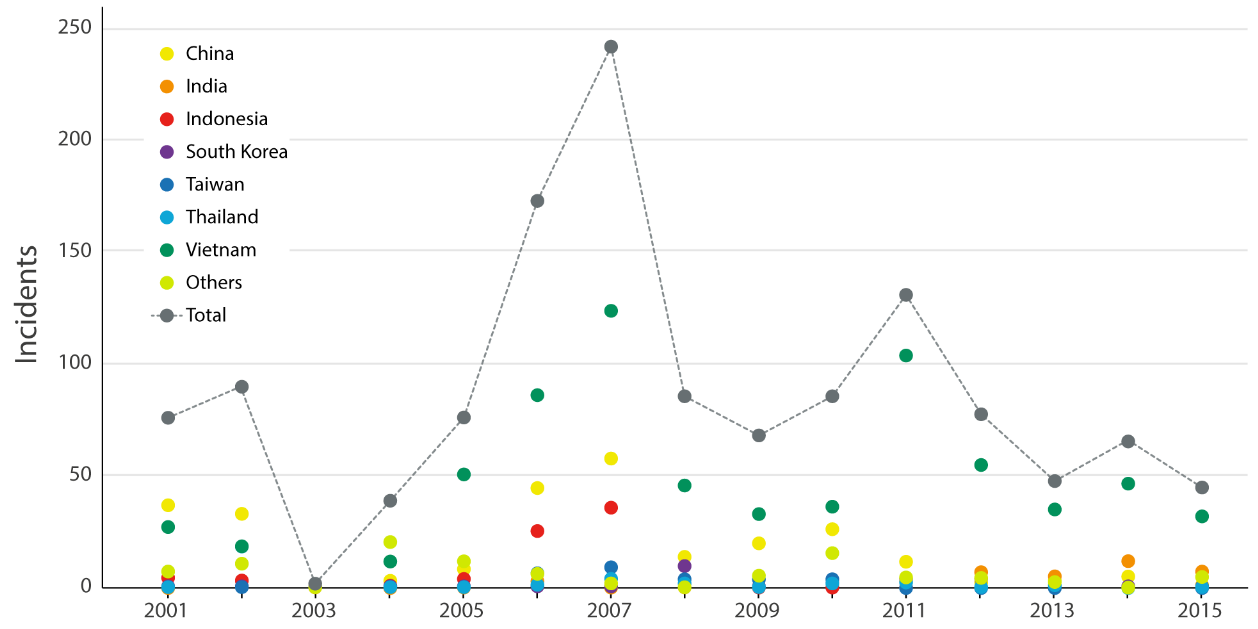
Vaccines can efficiently prevent bacterial diseases and a successful example is Norwegian salmon farming where vaccines have made it possible for reduction of antibiotics. Today less than 1% of the fish are being treated with antibiotics. Another example is the use of vaccines to address Grass Carp Hemorrhagic Virus in China. However, the salmon industry in Chile still depends on a large quantity of antibiotics due to e.g. presence of *Piscirickettsia salmoni*, for which no successful vaccine has been developed. Use of antibiotics in Chilean salmon farms therefore exceeds usage in salmon farms elsewhere. Vaccines have also been developed in other aquaculture sectors but with less success.



Comparison of antibiotic use in salmon production in main producing countries.

Box 2: Shrimp

The shift from traditional to semi-intensive and intensive shrimp farming in Asia has resulted in increased disease outbreaks with consequent additional use of antibiotics. Since shrimp is a commodity primarily destined for export, importing countries have strengthened residue-testing programs for antibiotics. This resulted in an increased rejection rate of shipments and even EU bans on shrimps from certain countries (i.e. after detection of e.g. chloramphenicol and nitrofurans residues). A shift towards farming whiteleg shrimp (*Litopenaeus vannamei*) and use of pathogen-free seeds has reduced use of antibiotics. However, new diseases have recently emerged (e.g. Acute Hepatopancreatic Necrosis Disease (AHPND) and Enterocytozoon hepatopenaei (EHP)) incentivizing increased use of antibiotics.



The number of reported incidents in EU, US, and Japanese customs involving antimicrobial residues. The data are not reported consistently, resulting in some discrepancies, for instance the lack of reported cases in 2003. (Sources EU's Rapid Alert System for Food and Feed, US's Food and Drug Administration, and Japan's Ministry of Health, Labour and Welfare)

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