Beyond the Plate: The Wider Impact of Antibiotic Use in Salmon Farming

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Article:
From a fresh Japanese salmon nigiri to being the best component of any brunch, salmon is integral to the culinary identity of cultures across the world. To meet the global demand for salmon in the 21st century, suppliers shifted from sourcing fish solely from wild-caught populations to raising stocks artificially. While aquaculture—which is just farming while wet—developed thousands of years ago, the practice has only truly become integral to global food production in the past 70 years: farmed fish yields have increased from less than 1 million tons of fish in 1950 to over 80 million tons in 2017[1]. Of farmed fish, salmon represent the highest production growth on the market[2]; their success in the aquaculture world cements their position as a global staple and a sound investment for farmers, meaning this species will surely continue to dominate the food market for years to come. Dr. Chloé Fouilloux, a postdoctoral researcher based at the University of Wisconsin, Madison aims to understand how current aquaculture farming practices may unintentionally shape the evolution of both human and animal health.

While farmers have taken to raising salmon in captivity, there is the very real challenge of finding a way to mass produce a (genetically) wild aquatic animal. Salmon are tricky. Unlike cows or chickens, which have been domesticated through the process of artificial selection for ten thousand years[3] salmon are still 'wild' animals. These fish are one of those long-distance migratory species that spend their juvenile years in freshwater, swim to the ocean to spawn, and return to their birthplace in an epic final act—swimming themselves to death for their one and only chance to mate[4]. It is hard to replicate a salmon's epic quest in artificial conditions. Typically, farmed salmon are reared in distinct stages: eggs develop in heated (to shorten development time) terrestrial freshwater tanks from which juvenile salmon are transferred to a marine environment, often in pens within a bay or a fjord (called mariculture, Fig 1) where they remain for several years until they are harvested[1].

By maturing salmon stock in diverse waterways, farmers take advantage of the inherent chemistry and physiological properties (e.g., currents, temperature) of natural environments to create suitable housing conditions for their livestock. However, in using open net cages there are no solid barriers distinguishing farmed salmon from their surrounding environment, which has many implications for their interactions with wild salmon and other fish and predator species[4]. While the issues in livestock farming are far from being singular, the impact of salmon farming on marine ecosystems can be distinguished from terrestrial practices as (1) animal pens are built directly into the natural ecosystem, (2) farmed species may interact and breed with wild species (which has both genetic and disease transmission implications[5]), and (3) the input of chemical compounds and byproducts of livestock are directly funneled into globally connected waterways.

The last point is of particular research interest, where, for example, the application of antimicrobials as therapeutic treatments for salmon creates a scenario where non-ingested or unabsorbed medication (which can persist in the environment for days to months[6]) is indiscriminately transported from pens into wild habitats, medicating non-target fauna. In this featured WISL project, Fouilloux explores the effects of salmon fisheries on the presence of antimicrobial resistance (AMR) in wild fish populations throughout the Vancouver Island area. Having grown up by the water, Fouilloux was raised catching and eating fish and crustaceans—this is just one of the many reasons she is interested in how good food and human health coexist in an era where farming practices are increasingly dependent on pharmaceuticals.

The use of antimicrobials in aquaculture

For many reasons, sometimes because of stress, high rearing densities, or cross-contamination, salmon get sick. While getting sick is a normal and unavoidable part of life, for a farmer, disease can incur costs to the gross amount of their market-quality output. As with any cultivated species, ranging from cows to corn, a farmer's objectives are identical: maximize size, yield, and perhaps most importantly, maintain a healthy, fit-for-consumption product.

Not many would be interested in eating a cow with mad cow disease or rotten corn.

In efforts to both prevent and treat disease in aquaculture, many farmers treat salmon with antibiotics to prevent the growth of bacterial pathogens. Treating aquatic animals is no easy feat. Your patient is difficult to access, not a huge fan of being handled, and dies after being outside of their preferred environment for more than a couple of minutes. Based on these limitations, it is not surprising that administering medication via medicated feed is the most common option for treating salmon. Unfortunately, it is terribly ineffective. For example, the antibiotic oxytetracycline (OTC), used to treat pneumonia and UTIs in humans, is commonly applied both as a preventative and as a remedy to disease in fisheries. Yet, up to more than half of the applied dose ends up unabsorbed in the water[7,8]. The circumstances under which antibiotics are needed can lead to rushed diagnoses to salvage diseased farmed stock, meaning that the administration and regiments of drug use can be inappropriate for the actual disease[5]. This problem is further exacerbated by the administration of drugs being largely unmonitored and without consistently enforced limits on a global scale[9].

Why the use and overuse of antibiotics matters

Antibiotics are our most powerful biomedical weapons: since their discovery one hundred years ago, these compounds have become the heart of modern medicine. Yet our dependence on these compounds has quickly backfired, as the application of antibiotics inevitably selects or leaves behind bacteria that can survive in the presence of these powerful chemicals. These survivors are categorized as having "antimicrobial resistance" or AMR, which has been part of our global parlance for the better part of two decades. In our recent history, AMR is the (unintended) selection of certain microbial genes that ensure that microbes can resist the effects of antibiotics [10]. From a human perspective, this selection has snowballed into a world-wide struggle to eliminate pathogenic bacteria that are resistant to medicine that once would have killed them. What happened? Numerous complicated factors muddle the story, but the over-administration of drugs (in both humans and livestock), inconsistent or incomplete treatment plans by patients, and increasing the strength/dose of medicine (which indirectly selects for stronger bacteria) have all come together in shaping the global crisis of antibiotic resistance that we currently face.

The gravity of antibiotic resistance cannot be understated: each year, over 700,000 people die from treatable diseases as microbial strains evolve resistance to drugs that were previously effective[11]. This trend is rapidly increasing (est. 10 million annual deaths by 2050[11]) and diversifying to different antibiotic combinations, further limiting our ability to treat once manageable diseases. We are already feeling the consequences of this public health challenge. From 2000 to 2015, the global daily dose of antibiotic consumption increased 65 percent[10]. By increasing both the dose and the frequency with which we take antibiotics, we make their consumption more dangerous while also reducing their long-term efficacy. Thus, we are caught in a vicious arms race between attempting to slow the spread of resistance while keeping our loved ones healthy.

This same process also plagues farmed animals. Chickens are intensively treated with antibiotics--both to increase growth and to prevent infection. Overall, poultry are exposed to 4 times as many antibiotics as cows[12,13]. Unsurprisingly, these usage rates are strongly correlated with the rise of antibiotic resistance, and the microbiomes of farmed animals harbor genes that confer antimicrobial resistance[13]. The same trend holds true for aquaculture. Chile, one of the world's largest exporters of farmed salmon, is plagued by "super resistant" bacteria found in fishes with mutated genes enabling them to resist broad spectrum antibiotics[9]. These multi-resistant bacteria accumulate in the intestines of fish and are excreted with feces, dispersing antibiotic-resistant bacteria to the wild of the oceans.

Overall, the chemical structure of antibiotics makes them resistant to degradation, giving these molecules the opportunity to both persist and accumulate in natural habitats[14] and impact non-target species. Further, most antibiotics are both water soluble and readily excreted with metabolites (i.e., feces), meaning that these compounds can easily enter and disperse through the environment. To some degree, our society is aware of the cascading effects of mismanaged drug disposal, which we have seen in both virally circulated stories, such as the sex-reversal of fish resulting from accumulated birth control hormones in water[15] to the generation-defining mythology of the *Teenage Mutant Ninja Turtles*, a band of crime-fighting New York reptiles exposed to toxic sewage. Although in their initial form antibiotics are designed to save lives, the mishandling and incomplete disposal of these compounds have made them an increasingly troublesome source of environmental pollution[16].

There is evidence establishing the relationship between antibiotic runoff and AMR in wild populations, where for example, sea floor samples taken from varying distances from fish farms report bacteria resistant to penicillin, quinolone, and tetracycline[21]. If any of these antibiotics sound familiar, that is the crux of the issue: some antibiotics used in treating salmon are also used in human medicine[5]. One of Fouilloux's goals is to understand the extent to which wild species are impacted by AMR spillover (and how these rates change as a function of environmental conditions, for example). Assessing spillover is based on quantifying the rate of AMR gene accumulation in wild fish populations. In the context of Dr. Fouilloux's project, this hinges on analyzing DNA extracted from gill swabs from the three-spine stickleback, *Gasterosteus aculeatus.* These fish were sampled from lakes of varying distances to commercial fisheries throughout Vancouver Island. Once having extracted DNA from swabs, Fouilloux uses cutting-edge bioinformatic sequencing approaches to analyze bacterial DNA and monitor the abundance and diversity of AMR genes. Initial sequence analysis of bacterial genomes has revealed the presence of AMR genes in the gill microbiomes of three-spine stickleback, demonstrating the real-time impact of AMR-spillover from anthropogenic sources around Vancouver Island.

Having established the presence of AMR-genes in wild populations, over the next two years Fouilloux aims to understand how the ecology and land use practices of the region inform AMR accumulation in the wild. In collaboration with Dr. Jessica Hite from the University of Wisconsin, Madison, Fouilloux will use structural equation modelling and various spatial analyses to understand how environmental and anthropogenic factors (i.e., distance from salmon farms, hydrogeographic data) interact to shape the risk of wild fish populations acquiring AMR. For example, Fouilloux hypothesizes that specific habitat characteristics, such as lake depth and water flow, interact in escalating or dampening the impact of AMR accumulation in the environment. Once having identified the factors that drive differences in accumulation rates, these data will provide fundamental, empirically derived models that can be used to forecast how land use change (like establishing a new logging site) or climate change (i.e. El Niño versus La Niña years) may impact AMR rates in the wild. This knowledge provides the framework to enact policy changes, such as restricting activity during specific seasons in vulnerable areas, to protect the welfare of both fauna and farmers.

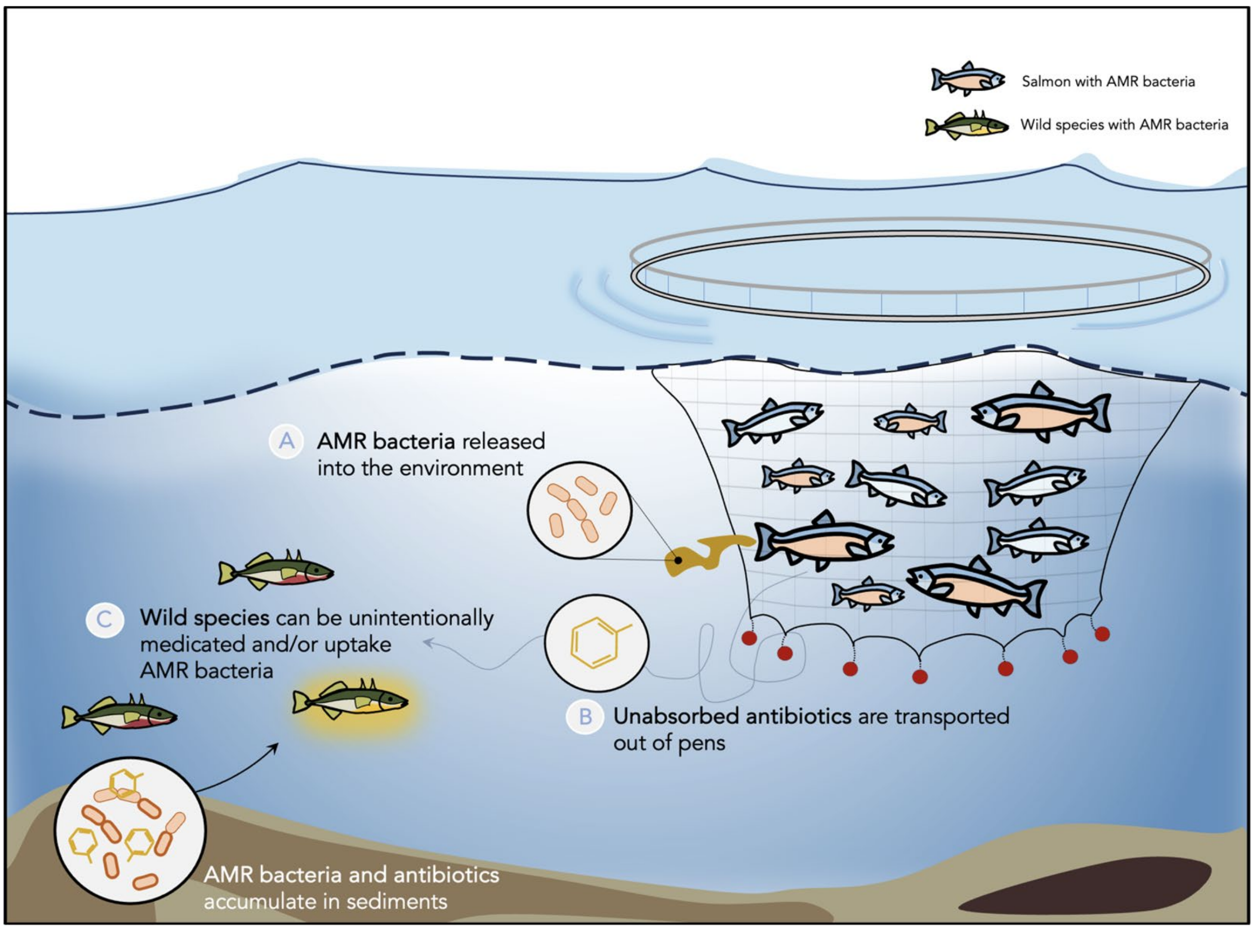

Figure 1. The impact of aquaculture antibiotic use on wild populations. Farmed salmon enclosures exist in connected aquatic habitats that allow applied and metabolized chemical compounds to escape the confines of pens. Antimicrobial resistance (AMR) in farmed salmon is a common issue, but the downstream effects of the spread of AMR bacteria through metabolized waste (A) and unabsorbed compounds (B) have diverse and poorly understood implications for the transmission of AMR in wild species (C).

The unintended targets of antibiotics

As with the mutant New York turtles, who were unintentional victims of mishandled drugs, the overapplication of antibiotics in hospitals and farms can impact the microbial communities of wild populations. In an unfortunate evolutionary twist of fate (and analogous to the aforementioned teenage turtles), antibiotic resistance genes are masters of movement, showing an uncanny ability to incorporate themselves into mobile genetic elements (i.e., plasmids, transposons) which are special segments of DNA that can either move around within a genome or migrate to a new genome (generally achieved by encoding enzymes). These mobile DNA can override previously coded functions or introduce new functions, like providing instructions for resistance to specific drugs. In the wild, bacteria especially have a funny habit of taking up these free-floating mobile genetic elements and incorporating them into their own genome[17]. This means that AMR genes, which can be dispersed via rivers, sediments, and feces, can swiftly become represented in distant naïve host populations[9,14]. This can visually be summarized as a Russian nesting doll of genetic hijacking, where AMR genes become incorporated into mobile genetic elements, mobile genetic elements jump into a bacteria's genome, and this newly acquired resistance passes onto future bacterial generations (Fig. 2).

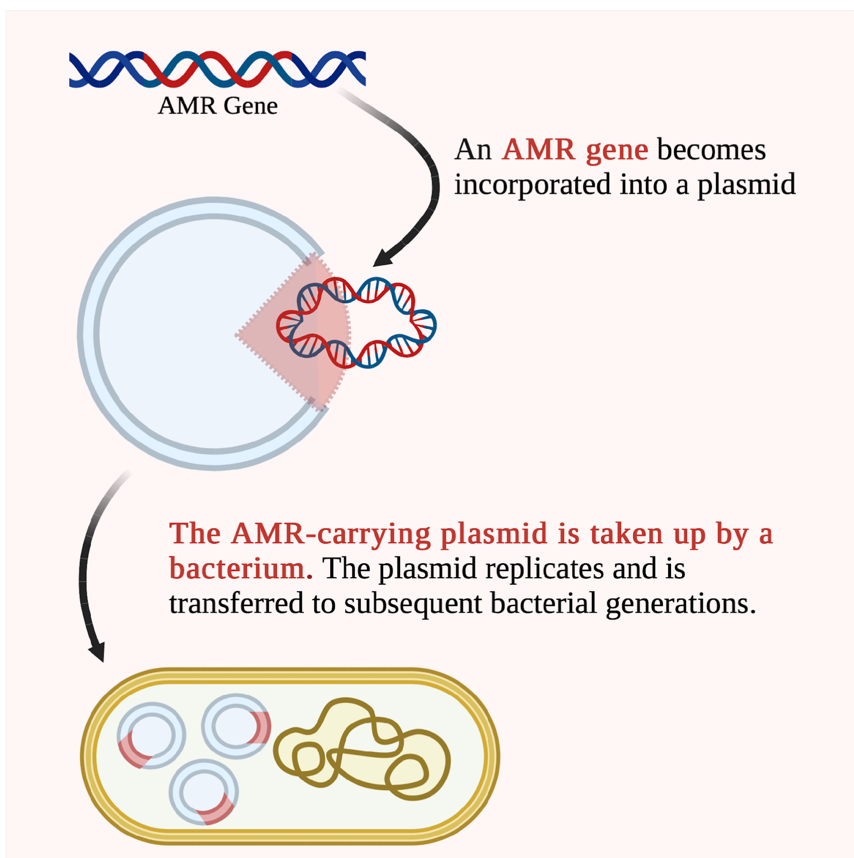

Figure 2. The Russian nesting doll of genetic hijacking. DNA carrying AMR-gene mutations can be readily taken up by mobile genetic elements, such as plasmids. In this example, a plasmid (along with its newly acquired AMR) enters a bacterium through a process called transformation. As bacteria multiply, AMR genes contained within plasmids persist within and spread throughout bacterial populations.

As with the Russian doll, where smaller elements are incorporated in consecutively larger ones, AMR bacteria can move from being in the environment to being in the bacteria (both pathogenic and nonpathogenic) that make up the microbiomes of other species. Mechanistically, the transmission of AMR within and across species of bacteria (termed horizontal gene transfer) and their ability to colonize different hosts, including humans, is becoming increasingly recognized as a primary route for disseminating AMR. Once an organism acquires resistance to a specific antibiotic, this means this class of drug is no longer effective at killing bacteria that it could previously destroy. Because antibiotic classes are grouped by shared structure and resistance pathways, the resistance to one can compromise effectiveness of many others, further limiting treatment options for AMR afflicted individuals[24].

Considering the connectivity of sewage systems and waterways and the relative ease with which bacteria acquire AMR genes, the effects of aquaculture practices on the spillover of AMR to wild populations is especially concerning. In a world where AMR is becoming increasingly problematic for human medicine, Fouilloux says that understanding how resistance spreads between species will be key to unlocking interventions to safeguard the efficacy of antibiotics in the future. Appreciating the extent to which natural communities are impacted by seemingly unrelated agricultural and clinical practices is fundamental to highlighting the breadth of the AMR crisis, which clearly requires global coordination to achieve quantifiable impacts.

Antimicrobial resistance in wild populations: A world full of Mutant Ninja Turtles?

Antibiotics escape into the surrounding environment, persist for weeks in the water column, accumulate in sediments, and these contaminants select for drug resistant bacteria that can transmit to new wildlife hosts. What does it mean that wild animals may accumulate antibiotic resistance? *It is not that the salmon themselves are acquiring AMR, but the bacterial communities that exist within them.* Although this may seem like a separate world, we are a sum of our parts. Updated estimates report that the balance between bacteria and human cells within an organism is essentially 1:1, meaning that we contain as many bacteria as we do. . . human stuff[22]. Thus, if the bacterial community of an organism has acquired AMR, by any meaningful metric it is reasonable to say that the animal-host has acquired this resistance as well.

There are multiple potential outcomes with troubling implications. First, wild salmon may serve as the vectors for transmission of AMR pathogens that spill over to other animals (including humans). Marine stock pens are a magnet for wild species, mostly because of the free food, and the exchange of diverse pathogens has been documented multiple times[4,5]. On their migratory routes, wild fish can become reservoirs for a multitude of antibiotic resistant pathogens[7], spreading resistant strains to new farmed populations as they migrate. This means farmed salmon can acquire new types of antibiotic resistance from passing wild populations. To keep AMR-impacted fish healthy, farmers may try increasing the applied dose of antibiotics or finding a new drug to which the stock is not resistant-- either option results in the increase in the total amount or the diversity of drugs present in fish tissue that we consume. In addition to animal welfare and affecting the evolution of pathogens in the environment, wild salmon and other fishes can acquire antibiotic-resistant bacteria that can be directly transferred from animals to humans[13,23], conferring resistance genes to our own microbiota. Scientists are still investigating the impacts of food-transmitted AMR pathogens through the consumption of uncooked fish or contact with contaminated materials, "We are unsure how this may directly impact human health", Fouilloux comments, "and as a result of the potential impacts, this is an area of very active research."

What does this all mean? Should you stop enjoying smoked salmon on a lightly toasted bagel? Are all wild species eventually doomed to acquire AMR genes, rendering antibiotics ineffective and crumbling our modern medical system[10]? While all the outcomes above have been proposed as dystopian futures, it is also true that global action is being taken to aggressively decrease antibiotic usage, with some projections predicting antibiotic use to be halved in the coming years[9]. While these hopeful projections should be tempered with a nihilistic optimism, consumer pressure has been a genuine force of change in the food industry in the past, reducing the amount of human-use antibiotics on large commercial farms (e.g., Tyson, McDonald's[25]).

With increased reporting and transparency about drug administration in the aquaculture industry, scientists will be better able to predict the downstream impacts of AMR acquisition in wild populations. Finally, technological innovations in the aquaculture sector are frequent, and increased consumer awareness has emphasized development of more sustainable mariculture options[26]. Altogether, while the escalation of AMR is a very real and pressing threat, it is important to remember that the development of antibiotics was one of the greatest discoveries of the 20th century-- perhaps developing mechanisms to safeguard them from widespread resistance will be the crowning success of this century.

As Raphael from the Teenage Mutant Ninja Turtles once said, "*It's not about the size of the turtle in the fight, it's about the size of the fight in the turtle.*"

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