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Antibiotic Use in Finfish Aquaculture: Modes of Action, Environmental Fate, and Microbial Resistance

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Abstract Various antibiotics have been used over the past 20 years and continue to be registered for use in finfish aquaculture in the United Kingdom, Norway, Ireland, and Canada. These include β-lactam (Amoxicillin), macrolide (Erythromycin), phenicols (Florfenicol), quinolones (Oxolinic acid, Piromidic acid, Naladixic acid, Flumequine), fluoroquinolone (Sarafloxacin), sulphonamides (potentiated sulphonamides), and tetracyclines (Oxytetracycline). Vaccines have largely replaced antibiotics as a means for controlling bacterial pathogens in cultured finfish but these anti-microbial agents continue to be applied to control disease in both hatcheries and grow-out stock. Bacterial strains resistant to specific antibiotics used in aquaculture have been cultured from mixed microbial communities in sediments after treatments of cultured fish stocks with antibiotics cease. This chapter considers modes of action, factors affecting environmental persistence and ecological aspects of antibiotic resistance of the major antibiotics currently used in finfish aquaculture in Canada and Europe.

Keywords Antibiotic resistance · Disease control · Microbial infection · Salmon aquaculture · Waste feed and feces

1
Introduction

The high biomass of finfish cultured within the restricted volume of netpens creates the potential for microbial and parasitic infections. The risk is so great that animal health management is a central husbandry requirement in all finfish aquaculture operations [1, 2]. Although the development of standard codes of practice, improved biosecurity and the use of vaccines have resulted in reduced use of antibiotics from levels used a decade ago [3–8], chemotherapeutants continue to be used. Diseases and infections will always need to be controlled to ensure maximum production [1]. Here we review various antimicrobial agents used to control infectious bacterial diseases in finfish aquaculture. Mode of action, persistence, and concerns surrounding the development of antibiotic resistance as they relate to environmental and human health are presented.

2
Types of Antibiotics

A small number of antibiotics are registered for legal use in the finfish aquaculture industry in Canada and Northern Europe (Table 1).

2.1
β-Lactams

β-Lactam antibiotics such as Amoxicillin (Fig. 1) interfere with the enzymatic cross-linking (i.e. transpeptidases and carboxypeptidases) of the cell wall in actively growing bacteria. The activity of β-lactams depends on the affinity for the target, permeability constraints such as bacterial capsule and peptidoglycan, and the stability of β-lactamases. β-Lactamases can be regulated by constitutive or inducible mechanisms [9, 10]. Amoxicillin is typically used for the control of furunculosis in salmonids caused by *Aeromonas* sp. It is administered orally in medicated feed at a dose of 80–160 $\mathrm{mg\,kg^{-1}}$ body weight $\mathrm{d^{-1}}$ for a standard period of 10 days [11]. The withholding period for β-lactam antibiotics in the United Kingdom is 40–150 degree days in Atlantic salmon (*Salmo salar*). Environmental concerns with respect to persistence of the β-

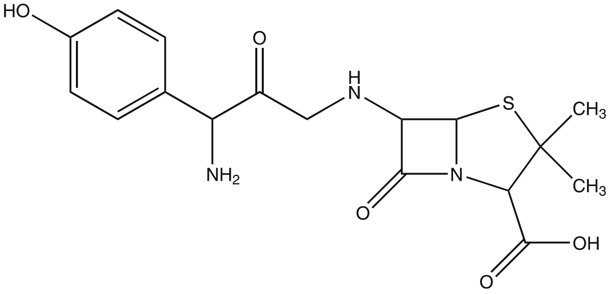

Fig. 1 Chemical structure of Amoxicillin

Table 1 Antibiotics used in the aquaculture industry in Canada, United Kingdom, Ireland, and Norway

Canada[1]	United Kingdom	Ireland[2]	Norway
Florfenicol	Florfenicol		Florfenicol
Oxytetracycline	Oxytetracycline	Oxytetracycline	Oxytetracycline
Potentiated sulphonamides	Potentiated sulphonamides	Potentiated sulphonamides	Flumequine
	Sarafloxacin	Sarafloxacin	Oxolinic acid
	Anoxicillin	Anoxicillin	

[1] [7, 12, 13]

[2] Four antimicrobial agents were used in Ireland up to 2001 – OTC, flumequine, anoxicillin, sulphadiazine potentiated with trimethoprim (Sulfatrim) [5]

lactam group of antibiotics are minimal. β-Lactams should be susceptible to biological and physicochemical oxidation in the environment since these are naturally occurring metabolites with an amino acid synthetic base.

2.2 Macrolides

Erythromycin is a broad spectrum antibiotic produced by the bacterium *Streptomyces erythreus* (Fig. 2). Erythromycin interferes with bacterial protein synthesis by binding to the 50S subunit of the bacterial ribosome with increased activity towards Gram positive micro-organisms primarily due to steric effects. It is successfully used against bacterial kidney disease (BKD) which is caused by *Renibacterium salmoninarum* in salmonids. Erythromycin, typically is provided in feed at a dose of 50–100 $\mathrm{mg\,kg^{-1}}$ body weight $\mathrm{d^{-1}}$ for approximately 21 days in which this dose reduced BKD mortality in brook trout by 50% [14]. No withholding period for this group of antibiotics has been recommended because erythromycin is not approved for

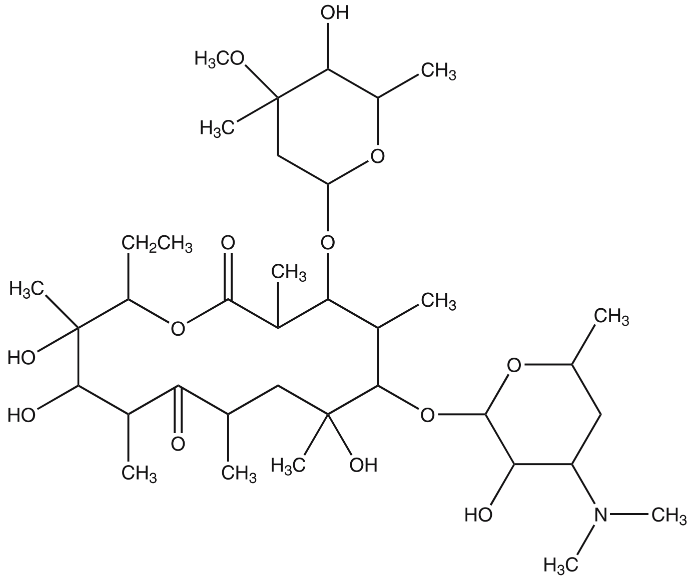

Fig. 2 Chemical structure of Erythromycin

use in International Council for Exploration of the Seas (ICES) countries. However, an excretion level of 0.03–0.08 mg g^{-1} was determined 168 hours after cessation of a treatment protocol of 50 mg kg^{-1} d^{-1} for 5 days in yellowtail [14]. Acute toxicity of erythromycin in excess of 2 g kg^{-1} was minimal with no abnormalities noted. However, when rainbow trout were subjected to a regime of 100 mg kg^{-1} d^{-1} for 21 days, behavioral and physiological abnormalities appeared.

The environmental effects of erythromycin may be more related to antibiotic resistance than to persistence since the ether linkages within the molecules will be susceptible to reduction or oxidation by physicochemical or biological processes. Although soluble in water and alcohol (2.1 mg ml^{-1} and > 20 mg ml^{-1}, 28 °C, respectively), the compound still has the potential to become associated with particulate matter, bioaccumulate in organisms and concentrate in sediments with potential effects on the micro-organisms.

2.3
Phenicols

Florfenicol acts as a broad spectrum antibiotic against Gram positive and Gram negative bacteria by binding to the 50S ribosomal subunit to prevent protein synthesis [15, 16]. Florfenicol has a fluorine atom instead of a hydroxyl group located at C-3 seen in the structure of chloramphenicol and thiamphenicol (Fig. 3) [17]. This structural change makes florfenicol less sus-

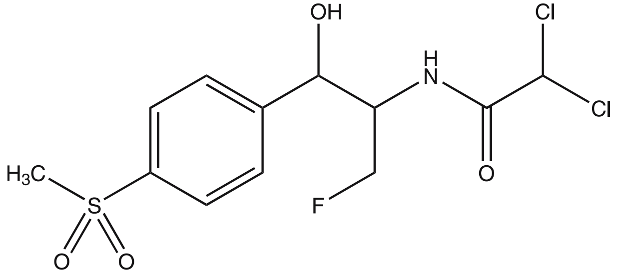

Fig. 3 Chemical structure of Florfenicol

ceptible to deactivation by bacteria with C-3 acetylation plasma-transmissible resistance and prevents interaction with bacterial ribosomes.

Florfenicol is used for treatment of furunculosis in salmon caused by *Aeromonas salmonicida* [18]. Exposure periods are usually 10 days at concentrations of 10 mg kg^{-1} body weight d^{-1}, with no adverse reactions seen at 10 times the normal dose for a 10 day treatment period. The withholding period is 12 days, 150 degree days, or 30 days for Canada, United Kingdom, and Norway, respectively. Withdrawal time for *Salmo salar* in Canada is 12 days, however the water temperature must be over 5 °C.

The adsorption of Florfenicol in *Salmo salar* is 96.5% with a dose of 10 mg kg^{-1} at water temperatures of 10.8 ± 1.5 °C [15]. Florfenicol was distributed throughout all tissues and organs in *Salmo salar* at a dose of 10 mg kg^{-1} d^{-1} when water temperature was 8.5–11.5 °C [18]. Florfenicol concentrations in muscle were similar to those in blood and serum concentrations, while central nervous system and fat tissues had lower concentrations. Only 25% of serum concentrations were found in the brain. The half-life of Florfenicol when administered intravenously was 12.2 hours at a water temperature of 10.8 ± 1.5 °C [15]. Florfenicol degrades in the sediment with a half-life of 4.5 days and it displays low toxicity to aquatic organisms [19, 20]. There is low bacterial resistance to florfenicol and therefore it should not present a serious environmental concern in terms of persistence and induction of resistance.

2.4
4-Quinolones

The 4-quinolones are a relatively new group of antibiotics that are predominately active against Gram negative bacteria. However, future generations of quinolones may be developed that are effective against Gram positive bacteria, anaerobes, and some protozoa. Four quinolones are commonly used in the aquaculture industry: Oxolinic acid (Fig. 4), Flumequine (Fig. 5), Nalidixic acid (Fig. 6), and Piromidic acid (Fig. 7).

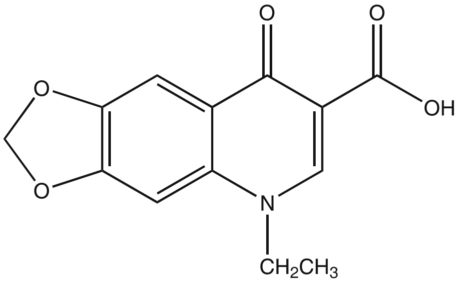

Fig. 4 Chemical structure of Oxolinic acid

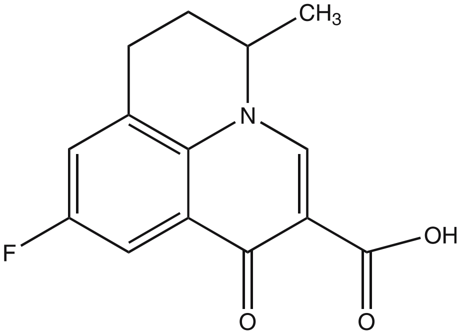

Fig. 5 Chemical structure of Flumequine

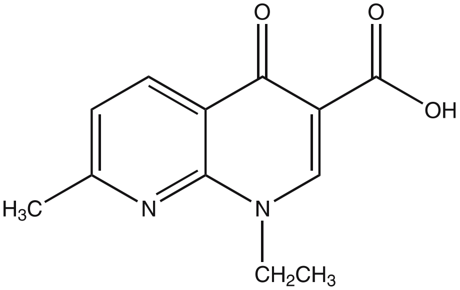

Fig. 6 Chemical structure of Nalidixic acid

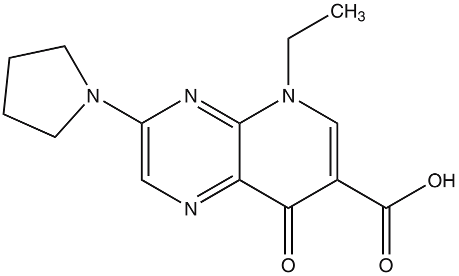

Fig. 7 Chemical structure Piromidic acid

The 4-quinolones are active against the bacterial DNA gyrase which acts by inhibiting the supercoiling of the bacterial DNA. Resistance to quinolone antimicrobials may not be plasmid encoded and requires the development and/or selection of genetic resistance. Withholding periods for this group of antibiotics, notably Oxolinic acid, are 500 degree days in the United Kingdom and greater than 80 days at less than 8 °C, 40–60 days at 8–12 °C, and 40 days at greater than 12 °C in Norway.

The 4-quinolones are new antimicrobials which have a high efficacy and relatively low toxicity. However, these anthropogenic compounds are not susceptible to enzymatic degradation or transformation, since microbial populations have not had any selective pressure to evolve enzyme systems to metabolize these molecules [20]. Therefore, these antibiotics have the potential to accumulate in aquatic environments. The 4-quinolones are susceptible to photolysis, however, this would be reduced under a fish cage in the presence of high suspended particulate loads or dissolved organic matter [21]. Furthermore, since these molecules attach readily to particles that eventually settle and accumulate in sediments, the probability of photolysis is low [22].

2.5
Fluoroquinolone

The fluoroquinolone Sarafloxacin is a water soluble antibiotic that is active against Gram negative bacteria [23, 24]. Sarafloxacin (Fig. 8) is rapidly absorbed by bacteria and it inhibits the action of DNA gyrase. It is typically added to feed at 10 mg kg^{-1} body weight d^{-1} for a period of 5 days. The withholding period after treatment is 150 degree days in the United States.

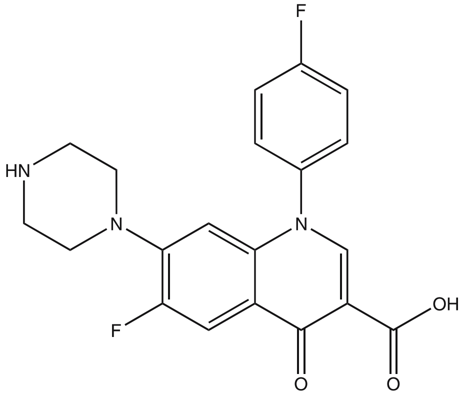

Fig. 8 Chemical structure of Sarafloxacin

2.6
Sulphonamides

The sulphonamides are a large class of antibiotics which are widely used in aquaculture to control furunculosis (*Aeromonas salmonicida*), enteric redmouth (*Yersinia ruckeri*), and vibrosis (*Vibrio* spp., *Cytophaga* spp., *Flexibacter* spp.) [25]. The most prevalent potentiated sulphonamide is Tribrissen (sulfadiazine: trimethoprim in a 5 : 1 ratio) (Fig. 9). Tribrissen inhibits dihydrofolate reductase whereas other sulfonamides, such as sulfadiazine (Fig. 10), inhibit dihydropteroate synthetase. Both enzymes are involved in the folic acid synthesis pathway [26]. These antibiotics are administered to finfish in feed and to molluscs in hatcheries in bath treatments. The typical dose for Tribrissen is 30–75 mg kg^{-1} d^{-1} for 5–10 days. The withholding period for these types of antibiotics is 350 – 500 degree days in the United Kingdom and 40–90 days in Norway which is temperature dependent.

The environmental implications of release of this type of antibiotic into the environment are unknown.

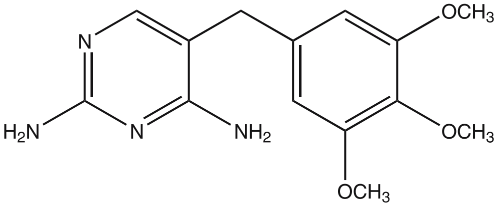

Fig. 9 Chemical structure of Trimethoprim

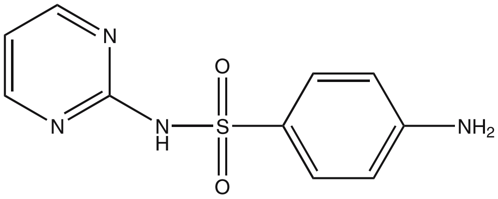

Fig. 10 Chemical structure of Sulphadiazine

2.7
Tetracyclines

The tetracycline antibiotic predominantly used in the finfish aquaculture industry is oxytetracycline (OTC) with trade names Terramycin Aqua in North America and Tetraplex in Ireland (Fig. 11). Technically Terramycin is the HCl-dihydrate and Tetaplex the HCL salt of OTC. Tetracyclines are bacteriostatic

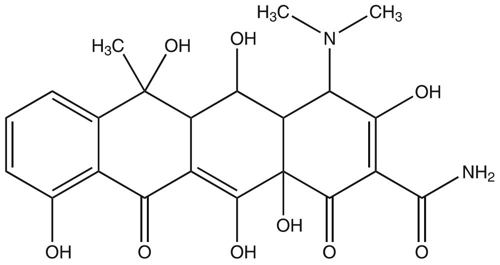

Fig. 11 Chemical structure of Oxytetracycline

antibiotics that interfere with protein synthesis by reversibly binding to the 30S ribosomal subunit, thereby blocking the binding of the aminoacyl tRNA to the mRNA/ribosome complex. They are broad spectrum antibiotics with activity against Gram positive and Gram negative bacteria. OTC is added to salmon feed at a dose of 50–125 mg kg^{-1} d^{-1} body weight for a 4–10 day treatment period [5, 27, 28]. Acute oral toxicity occurs at very low concentrations (LD_{50} values > 4000 mg kg^{-1}), about 50 times higher than the effective dose [29]. Treatment by antibiotic baths or injections is also performed. The withholding period for OTC in Norway is 60 and 180 days in water above 12 °C and below 8 °C, respectively. In the United Kingdom 400 – 500 degree days are required. Bacteria have a number of mechanisms to deal with OTC, which include proton-dependent efflux, ribosomal protection by cytoplasmic proteins, enzymatic degradation and rRNA mutations.

As discussed in the follow section, of all of the antibiotics used in finfish aquaculture, OTC has been most widely studied in terms of its fate, persistence and ability to induce antibiotic resistance.

3
Environmental Fate

Modes of administration and physical-chemical properties affect transport pathways, environmental fate and persistence of antibiotics in any aquatic environment where they are applied. From its inception the finfish aquaculture industry has used cost-effective means to mitigate microbial infections thereby minimizing the need for the added expense of medicated feed. However, when biosecurity and vaccination programs are either not available or not effectively applied, disease outbreaks inevitably occur and must be treated quickly and effectively. Typically antibiotics are administered orally with feed but direct injection and/or immersion in antibiotic bath solutions are also used. These methods are more time consuming and costly than administering medicated feed. The choice of treatment method is important since it influences local and far field transport pathways. Orally administered antibiotics associated with waste feed will generally be deposited under or close to the pens [5]. These particle-associated antibiotics will be available for ingestion by wild fish, and benthic suspension and deposit-feeding invertebrates. More water-soluble antibiotics and fish fecal matter can be transported considerable distances in the water column with potential effects distant from the site of application.

3.1
Persistence in Sediments

The addition of antibiotics in fish feed is the most common method of application. However, infected fish often have a reduced appetite making oral uptake a less efficient antibiotic treatment method than injection or immersion. Even if feeding rates are adjusted to minimize loss of uneaten food, the efficiency of antibiotic absorption may be low. The absorption rate of OTC across the gut wall by salmon is low ($< 2\%$ of the administered dose) and if digestion of consumed food in infected fish is further reduced, fecal matter would also be expected to contain increased concentrations of antibiotics [30–32]. Although husbandry practices can be adjusted to account for the possibility of reduced food intake, more unconsumed antibiotic-laden feed might be expected to be lost during feeding than normally occurs with healthy fish. Unconsumed antibiotic-treated feed pellets will then either be deposited and accumulated at a farm site or in high current areas may be distributed more broadly [33].

The effect of low assimilation and loss to the environment is reflected in attempts to construct mass balance budgets for OTC in the vicinity of salmon farms. Less than 8.5% of the total OTC input could be accounted for in sediments at farm sites where medicated feed had been applied [34, 35]. Similar estimates (1 to 5%) were made at four farm sites in Ireland [5, 36]. Since only a few percent of OTC input was accumulated in sediments and tissue samples from salmon and mussels at the farm sites, it was concluded that the ultimate sink for OTC was in dissolved and particle-associated phases in the water column. Water solubility leading to hydrolysis, advective transport and photo-reactivity led to the conclusion that OTC would not be expected to accumulate in sediments [37]. However, no study has directly measured OTC in water to track dispersion around a farm site following treated feed application.

Accumulation of antibiotics in sediments can occur either as a result of direct deposition of treated feed pellets under and in the vicinity of net-pens or by adsorption of antibiotics in dissolved or colloidal form onto settling particles [22, 38]. The relatively high water solubility of OTC [37] should reduce accumulation in bottom deposits, but any antibiotic remaining associated with particles could remain in sediments under fish cages for some period of time [39]. Accumulation is likely enhanced in sediments that are light and oxygen free, thereby preserving the structural integrity of the OTC [36]. OTC experimentally added to oxic marine sediments largely disappeared after a few weeks, but traces were detectable for up to 18 months [40].

Concentrations of OTC measured in coastal marine sediment at farm sites vary from $< 10\,\mu g\,g^{-1}$ [34, 41, 42] to a maximum of $240\,\mu g\,g^{-1}$ [36]. This can be compared to OTC concentrations in commercially prepared salmon feed pellets that are three orders of magnitude higher ($29\ mg\ g^{-1}$) [43]. OTC was found in fish farm sediments in Norway and Finland above detection levels ($10\,\mu g\,g^{-1}$) for periods of more than one year after treatment but these were primarily anoxic deposits associated with cage sites [34, 41]. High levels of bacterial resistance have been found in both sediment bacteria and isolates from intestines of wild fish around finfish aquaculture sites [34, 44]. This shows that while dispersion and dilution may reduce water concentrations to below detection limits, transport pathways exist for exposure of benthic invertebrates and demersal and pelagic fish to resistant strains.

In addition to physical-chemical properties, the persistence of antibiotic residues in sediments depends on several environmental factors among which sedimentation rates, the presence/absence of oxygen and water temperature are critical [20, 31, 34, 35]. The half-life of oxytetracycline in sediment was prolonged to 419 d under stagnant, anoxic conditions [34]. The half-life of Tribissen (20% sulfadiazine, 80% trimethoprim) at 6 to 7 cm depth was found to be 90 d while Florfenicol concentrations decreased more rapidly (t_{50} = 4.5 days) [20]. Shorter half-lives might be expected in more oxic sediments. Persistence of Tribissen was dependent on sedimentation rates at the site after medication [45]. The half-life of OTC of 72 d doubled to 135 days under a 4-cm layer of sediment, slightly longer than the average value (60 days) observed in mixed sediments several cm deep in an experimental laboratory study [38].

3.2
Ecological Effects in the Water Column

As discussed above, antibiotic injections are a direct and efficient way to administer treatment. Therefore, less antibiotic is used to treat each fish and losses to the environment are minimized. However, high labour costs usually preclude this approach even if treatment is more effective. Another method of application is immersion of infected fish in an antibiotic bath as described for sealice therapeutants [8]. The draw-back is that the bath solution must be released following treatment. Loss of OTC from the water column around a fish farm located in a salt marsh occurred in two phases with average half-lives of 30 h and 319 h, respectively [46]. Although the initial loss phase was relatively short, antibiotics remaining in the water column for even a relatively short time could affect planktonic organisms [47]. Physically removing or destroying antibiotics in solution before they are discharged could circumvent the problem but this added cost is usually avoided by simply releasing bath solutions after treatment.

3.3
Uptake by Biota

Bacterial communities involved with decomposition and mineralization processes of organic matter may be susceptible to exposure to antibiotics if concentrations accumulate in sediments [48]. Ecological effects of antibiotic treatment on microbially mediated sediment nutrient dynamics have been demonstrated [49]. A range of OTC concentrations (12.5 to 75 $\text{mg}\,\text{l}^{-1}$) were applied to quantify a dose-response relationship between OTC and nitrification in aquaria containing freshwater, sand sediments and catfish fingerlings. Nitrification rates, measured as decreases in ammonia and increases in nitrate concentrations over three weeks, were reduced by 50% as OTC concentrations increased from 8.6 to 30 $\text{mg}\,\text{l}^{-1}$, concentrations typical of doses recommended for bath treatment.

Several studies have shown that measurable concentrations of antibiotics appeared in non-target invertebrates either in the laboratory after exposure to residues in water and/or sediments or in close proximity to salmon cage sites where medicated feed had been used. During the years of high antibiotic use in the salmon aquaculture industry in Norway, fish and mussels near salmon farms contained OTC [50]. Since the half-life of OTC in mussels is short, estimated as approximately 2 days [5], the presence of residues indicated recent or continuous exposure. Oysters, crabs and benthic macro-invertebrates collected near salmon farms in British Columbia contained OTC and Romet 30 (5 : 1 sulfadimethoxine and ormetoprim) [35, 51–53]. The highest concentrations (3.8 μg OTC g^{-1} wet tissue) in rock crab exceed the guideline for seafood specified by the US Food and Drug Administration (2 $\mu\text{g}\,\text{g}^{-1}$) [35]. However, unlike the observations of suppression in bacterially mediated nitrification above, even at these relatively high concentrations no study has shown adverse effects of aquaculture-derived antibiotics on indigenous fauna.

4
Antibiotic Resistance

One result of the broad-scale release of antibiotics into coastal marine environments subjected to intensive aquaculture for either finfish or shellfish is the possibility for selection of resistance in non-target benthic organisms [54]. Mechanisms whereby microbial antibiotic resistance is induced have been summarized along with current methods for using microbial assays to quantify growth inhibition [55]. These methods have recently been standardized in an effort to make measurements of resistance more reproducible and quantitative [56].

Resistance to antibiotics has often been observed in natural bacterial communities in sediments near salmon aquaculture sites, but it may also be transferred to non-target organisms. For example, an increase in antibiotic-resistant bacteria in sediments occurred within a few days of treatment with OTC or Oxolinic acid [57]. High levels of resistance occurred at the end of the initial 10-day treatment when the percentage of resistant bacteria (ratio of numbers growing on substrate ± OTC) was $> 100\%$ in all sediment samples. OTC-resistant bacteria were isolated from the intestines of wild fish and rainbow trout that had fed on medicated feed [34, 41]. *Aeromonas salmonicida* has been identified as the source of resistance in salmon at 9 of 35 fish farms in Finland treated with OTC [58].

Resistance to OTC was detected in aerobic bacteria cultured from water, pelletized feed and fingerlings from freshwater Atlantic salmon farms in Chile [59]. High levels of OTC resistance [90% minimum inhibitory concentrations (MIC) up to 2000 μg OTC ml^{-1}] in selected strains suggested that salmon farms may be reservoirs for bacteria with high tetracycline resistance. Similar observations of OTC resistance, but with lower MIC values (up to 160 μg OTC ml^{-1}), were observed in surface sediments under and up to 100 m away from salmon farm pens in southwestern regions of the Bay of Fundy [60]. A standardized micro-dilution assay method was used to detect resistance in natural communities of bacteria isolated from sediment under pens and around various farm sites. Resistant strains, tentatively identified as *Psychrobacter glacincola* and *Psychrobacter pacificens*, were capable of growth in media containing up to 160 μg OTC ml^{-1} while a type culture of *Aeromonas salmonicida* used as a control showed no growth at 5 μg OTC ml^{-1}.

Results from field observations and experiments that demonstrate induction of antibiotic resistance should be treated cautiously since many factors can affect bacterial growth [46]. For example, species frequency data was analyzed and it was concluded that the operation of fish farms had minor long-term impacts on the size of bacterial communities in under-cage sediments [61]. This contrasts observations in Puget Sound where the number of colony-forming bacteria units were generally higher in sediments from cage sites than surrounding areas [62]. The proportion of OTC-resistant bacteria has also been observed to decline exponentially with increasing distance from a farm. Increased antibiotic resistance in sediments 75 m from the edge of a cage array in Galway Bay, Ireland was detectable during a brief (10-day) exposure to OTC [27]. However, after therapy ended, the frequency of resistance decreased exponentially, and within 73 days under-cage samples were not significantly different from background levels. In addition to husbandry practices that determine the release of medicated feed and fish excretory wastes to the environment, measures of antibiotic resistance in different studies will reflect various environmental and biological factors. Both the levels and persistence of microbial resistance observed in natural bacterial communities at and distant from any given farm can be expected to be highly variable and site specific.

Infectious micro-organisms were identified in sediments from an abandoned Norwegian salmon farm site [63] indicating that, irrespective of antibiotic use, once a disease outbreak has occurred, the probability of re-infection in a given area is increased. The development of antibiotic resistance may also have the potential for human health risk since positive correlations have been reported between antibiotic use and the isolation of drug-resistant bacteria in fish consumed as food [3, 64]. The successful transfer of antibiotic resistance was reported among strains of *Aeromonas hydrophilia* isolated from cultured *Telapia mossambica* via exchange of plasmids [65], illustrating the potential for the spread of drug resistance in cultured fish. The presence of OTC-resistant aeromonads in waters receiving hospital and aquaculture wastes [66, 67] also indicates that antibiotic resistance may arise from both human and aquaculture sources. Clearly, further studies are required to determine the extent of ecological and biological impacts of antibiotic resistance in microbial and other wild populations in areas of intensive finfish aquaculture.

5
Conclusions

Although many antibiotics are employed in the aquaculture industry their use should be restricted because of concerns over increased antibiotic resistance. The development of antibiotic resistance in natural microbial communities has the potential for far field effects on wild (non-target) species and indirectly or directly on human health. Furthermore, not all antibiotics employed in the aquaculture industry are equally persistent in the environment; aquaculture site managers must use their expertise to choose wisely the type, amount, and method of delivery of specific antibiotics to meet their needs. It is anticipated that good animal husbandry and environmental management will limit the need for the use of antibiotics in finfish aquaculture. Proper understanding of variables affecting the fate, transport and environmental persistence of these therapeutants should lead to changes in aquaculture husbandry practices that eliminate or greatly reduce the need to use medicated feed in the future.

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