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Veterinary drug use in United States net pen Salmon aquaculture: Implications for drug use policy

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ABSTRACT

Aquaculture now produces nearly half of the seafood consumed globally. Atlantic salmon (*Salmo salar*) is one of the top aquaculture products and the most valuable farmed marine finfish species in the United States (U.S.). The aim of this study is to better understand veterinary drug use in U.S. net pen Atlantic salmon aquaculture and compare these findings to other salmon producing countries and U.S. livestock. We collected and analyzed records on Atlantic salmon production and veterinary drug use in Maine (2003 to 2017) and Washington (2012 to 2017). Antimicrobial medicated feeds were used in 8% and 93% of production cycles in Maine and Washington, respectively. Oxytetratcycline was the primary drug used in both states. Maine used no antimicrobials in eight of the past 15 yrs., including none in 2017. Emamectin benzoate, an antiparasitic medicated feed, was used in 28% production cycles in Maine (2014 to 2017; avg. 1.1 kg/yr) and no emamectin benzoate was administered in Washington over the time period studied. From 2014 to 2016, the U.S. farmed salmon industry contributed 0.8% ± 0.1% to annual global farmed salmon production and administered 1.2% ± 0.6% of antimicrobials used in global salmon farming. Over the same time period, Norway and Chile accounted for 53% ± 3% and 35% ± 3% of annual global production, and administered 0.06% ± 0.02% and 96% ± 0.09% of antimicrobials used in global salmon farming. Compared to U.S. terrestrial agriculture in 2016, the U.S. Atlantic salmon industry contributed 0.031% to U.S. food animal production and administered 0.057% of antimicrobials available to U.S. food animals. Based on the data we collected, the U.S. Atlantic salmon aquaculture industry is a relatively small user of antimicrobials compared to U.S. beef, pigs, poultry, and Chilean salmon industries. There are relatively few approved drugs in the U.S. to treat aquaculture diseases and more options are needed as well as continued work on vaccines. Antimicrobial resistance is a worldwide public health concern; the overuse or misuse of antimicrobials in any setting can compromise the treatment of bacterial infections. The U.S. net pen Atlantic salmon aquaculture industry appears to be the first U.S. food animal industry to report monthly antimicrobial use at the farm-level to the government. These data are critical to assess public health risks associated with antimicrobial use and resistance, and therefore, are needed from all U.S. food animal industries.

1. Introduction

Atlantic salmon (*Salmo salar*) were first commercially farmed in the 1960s in Norway (Tilseth et al., 1991) and now salmon farming has become one of the most successful forms of aquaculture (Asche et al., 2013). Farmed Atlantic salmon are cultured first in freshwater hatcheries as fry and parr, and are then transferred to seawater as smolts or post-smolts for a grow-out period typically lasting up to two years. During the grow-out period, fish are reared in net pens, which are netted enclosures that are open to the surrounding aquatic environment that allow for water exchange and for uneaten feed and waste to leave the system. Over the past few decades, small salmon farms have been replaced by a handful of large, vertically integrated companies that use intensive farming methods that are comparable to the poultry industry (Asche et al., 2016; Torrissen et al., 2011). The global salmon industry produces over 2 million metric tons of fish each year, feeding millions

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of consumers in Europe, the United States (U.S.), Japan, and increasingly in East and South East Asia (FAO, 2018; FAO GLOBEFISH, 2018). The leading farmed salmon producing countries are Norway and Chile, and the U.S. ranks 7th (Undercurrents News, 2018).

The focus of this paper is U.S. production, where Atlantic salmon is the most valuable farmed marine finfish species, valued at $88 million in 2015 (NOAA, 2017). Maine and Washington are the only states in the U.S. where Atlantic salmon are raised commercially in marine net pens. There is growing interest among the U.S. government and the aquaculture industry to move finfish aquaculture onland or to waters further offshore (i.e., federal waters), in part to reduce a $14 billion seafood trade deficit (NOAA, 2017), spur economic activity, and potentially minimize some of the environmental externalities associated with nearshore salmon production (Rust et al., 2014). There are no Atlantic salmon farms currently in U.S. federal waters.

Disease is a top concern for the salmon aquaculture industry and a potential impediment to future growth (Lafferty et al., 2015; Stentiford et al., 2017). The major diseases impacting salmon production tend to vary by producing region, and within regions over time. In Washington, farmed salmon diseases known to exist include furunculosis (*Aeromonas salmonicida)*, yellow mouth (*Tenacibaculum maritimum*), vibriosis (*Vibrio* spp.), salmon rickettsial syndrome (SRS) (*Piscirickettsia salmonis*), and infectious hematopoietic necrosis (infectious hematopoietic necrosis virus, IHNV) (Personal communication, Washington Department of Fish and Wildlife). Washington fish are vaccinated for IHNV, *Vibrio* spp., and *A. salmonicida*; however, vaccinated fish populations can still be affected by clinical disease. There are no vaccines for SRS and yellow mouth, and the only treatment option is tetracycline (Personal communication, Washington Department of Fish and Wildlife). In Maine, reported farmed salmon diseases include bacterial kidney disease (*Renibacterium salmoninarum*) and infestation by sea lice *(Lepeophtheirus salmonis*) ectoparasites. Similar disease challenges exist in other salmon producing regions. Infectious salmon anaemia (ISA) has been associated with catastrophic losses in the Canadian Maritimes (1990s) and Chile (2000s), and while improvements in industry management have largely reduced the occurrence of this disease in both regions, its potential recurrence to previous levels remains a concern among producers. In Norway, reports of infectious pancreatic necrosis (IPN, associated with infectious pancreatic necrosis virus) have declined significantly over the past two decades, whereas pancreatic disease (PD, associated with salmonid alphavirus) has shown the opposite trend, and is now the most reported viral disease (Hjeltnes et al., 2018). Likewise, certain bacterial diseases that have historically impacted the Norwegian salmon industry (Lillehaug et al., 2003), such as furunculosis (*Aeromonas salmonicida*), cold water vibriosis (*Vibrio salmonicida*), and vibriosis (*Vibrio anguillarum*), are currently considered controlled, while other bacterial diseases, namely yersiniosis (*Yersinia ruckeri*) and winter ulcer (*Moritella viscosa*), as well as sea lice continue to be significant problems for the industry (Hjeltnes et al., 2018).

In intensive aquaculture operations, producers and veterinarians have a range of disease control options, including medicated feeds containing antimicrobials and antiparasitics, chemical baths, vaccines (for certain diseases), application of Labrid cleanerfish (fish used to remove sea lice from farmed salmon), mechanical methods (such as temporary changes in water temperature or salinity to combat external parasites), and efficacious biosecurity and husbandry practices (Noga, 2011). A relatively small number of antibacterial agents are registered for use in aquaculture in the U.S., Canada, and Europe. These include members of the following classes of drugs: macrolides (erythromycin), β-lactams (amoxicillin), fenicols (florfenicol), tetracyclines (oxytetracycline), quinolones (oxolinic acid), fluoroquinolones (flumequine) and potentiated sulphonamides (sulfadimethoxine/ormetoprim, sulfadiazine/trimetoprim) (Lunestad and Samuelsen, 2008; Metcalfe et al., 2008; Treves-Brown, 2013). The only drugs approved for use in the U.S. are oxytetracycline, florfenicol, and sulfadimethoxine/ormetoprim, which is a challenge for farmers because there are relatively few options available to treat diseases. These drugs are also from families listed as "critically important" or "highly important" for human medicine by the World Health Organization (WHO) (WHO, 2017b) and the U.S. Food and Drug Administration (FDA) (FDA, 2003).

A particular concern in connection with the use of antimicrobials is the development of resistant bacteria, causing antimicrobial resistance genes in the environment as well as the piscine and human microbiome. The development of antimicrobial resistance is a predictable, natural process and ancient among bacteria (Aminov and Mackie, 2007; D'Costa et al., 2011); however, the current global use of antimicrobial agents in human and veterinary medicine, including terrestrial animal agriculture and aquaculture, is an important driving force for increased antimicrobial resistance selection and evolution (Marshall and Levy, 2011). A reduction in the use of antimicrobials is possible through vaccination and improvements in husbandry practices, as shown in Norway (Grave et al., 1999; Simonsen et al., 2013). Managing fish health is crucial because of the linkages and interrelationship between human health, animal health, and ecosystems. This concept is known as One Health (Zinsstag et al., 2015) and is highly relevant when applied to food animal production and antimicrobial resistance (Cabello et al., 2016; Robinson et al., 2016).

Emamectin benzoate (EB) is an antiparasitic used to treat a fish parasite called sea lice that affects farmed Atlantic salmon in some regions. EB, known by the trade name SLICE ®, is the only chemotherapeutic of its kind approved for use in the U.S.; the other sea lice treatment used in the U.S. is a hydrogen peroxide bath. EB can have toxic effects on aquatic animals biologically similar to the target species, sea lice, such as crabs and lobsters (Tucca et al., 2014). The risk of impacts to nontarget species is increased due to slow degradation and potential build up of EB in the environment surrounding farmed salmon operations (Benskin et al., 2016). Sustained use of EB and similar compounds in countries with significant farmed salmon production have led to development of sea lice populations with reduced sensitivity to antiparasitics (Aaen et al., 2015; Lees et al., 2008). Sea lice infestations and reduced effectiveness of antiparasitics, including EB, has been identified as one of the most significant challenges facing farmed salmon companies around the world; sea lice may also facilitate bacterial infections and stimulate increased use of antimicrobials (Cabello and Godfrey, 2019). For example, a 2016 report on salmon health in Norway referred to the need for frequent, expensive sea lice treatments as causing an increase in production costs (Hjeltnes et al., 2017), and a study estimated that costs and losses associated with sea lice in 2011 was equivalent to 9% of Norwegian salmon farm revenues (Abolofia et al., 2017).

The aim of this study is to better understand veterinary drug use practices in the U.S. net pen Atlantic salmon aquaculture industry, which fills important data gaps. We hypothesize that antimicrobial use in U.S. salmon aquaculture is proportional to antimicrobial use in other Western countries with salmon aquaculture industries. To test this hypothesis we collected, digitized, and analyzed detailed records provided by state agencies on Atlantic salmon production and veterinary drug usage as well as from other salmon producing countries. We also compared salmon drug use to terrestrial food animals in the United States and discuss federal policy related to drug use and antimicrobial resistance.

2. Material and methods

2.1. Overview and scope

We collected data on Atlantic salmon aquaculture production and veterinary drug use from state and federal agencies using government websites, online databases, and personal communications. Data collection ran from November 2017 to May 2018 and covers the years 2003 to 2017. For the purposes of this study, we focused on marine net pen Atlantic salmon production, which occurs in Maine and

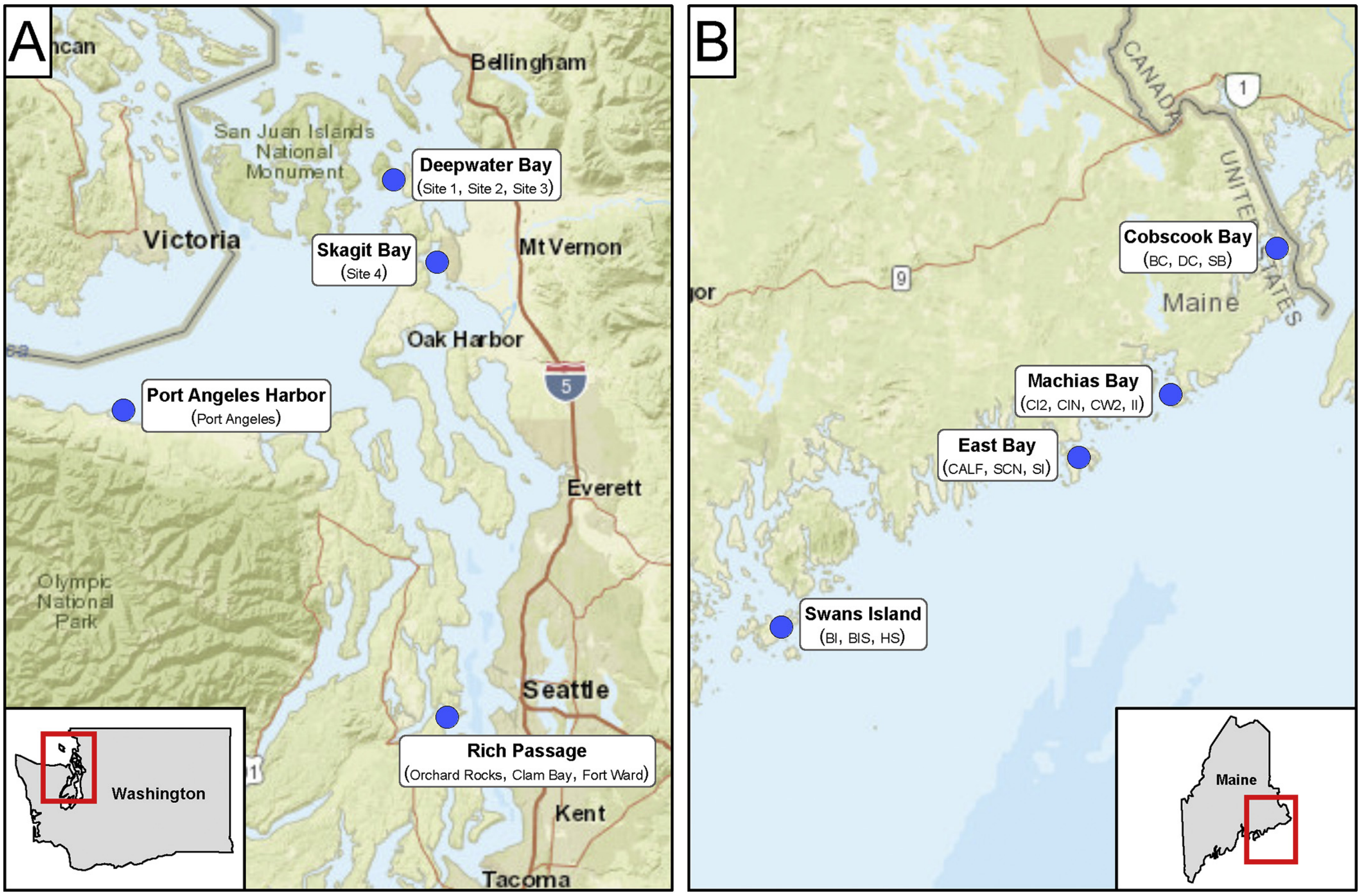

Fig. 1. Map of Atlantic salmon aquaculture sites in A) Washington and B) Maine, United States during the study period.

Washington, U.S. We excluded other salmonid species, such as freshwater trout because production methods vary considerably from Atlantic salmon. In addition, salmon raised in land-based recirculating aquaculture systems were excluded since it contributes little to overall domestic salmon production.

2.1.1. Washington, U.S

During the study period, Atlantic salmon in Washington were raised in eight production sites located in four geographic regions near the coastline (Fig. 1). A total of 102 net pens were available for production at all sites during the study period with a total permitted production volume of 14,470 metric tons (Table A.1). Each site had between 8 and 20 square pens arranged in a grid. Two locations in Washington, Deepwater Bay and Rich Passage, have the highest concentration of production, with three production sites clustered together at each location. Sites in Deepwater Bay are located roughly 250 and 400 m from each other, and in Rich Passage sites are located roughly 200 and 800 m from each other. Distance between net pen sites can be a factor in disease management, but the relationship between the use of veterinary drugs and density of net pen sites was outside the scope of this study.

Data on salmon production and veterinary drug use were provided by the Washington Department of Ecology (DE) via the online portal "Water Quality Permitting and Reporting Information System (PARIS)" (Washington Department of Ecology, 2018). The online portal is searchable by National Pollution Discharge Elimination System (NPDES) permit number and provides satellite images of farms, permit applications, correspondence between the DE and the permit applicant, and compliance reports. The permit holder provided DE with reports on monthly salmon biomass, monthly feed use, and monthly medicated feed use for each permitted site, however data at the pen-level was not reported. Monthly pdf reports from 2012 to 2017 were available and digitized in Excel (Microsoft, Redmond, WA) by the study team for further analysis. The database we analyzed is available in the Appendix.

The total biomass of salmon harvested in a given production cycle was not provided in regulatory reports. To estimate total biomass, we first determined the feed conversion ratio (FCR) for each production cycle. We used the total feed administered during a production cycle and the FCR to estimate the fish biomass added during grow-out in the pens, and summed the grow-out biomass and the biomass at stocking to obtain the total estimated biomass. Drug concentrations (grams per feed weight) were reported for 2012 to 2014, but not 2015 to 2017; therefore, an assumption in our analyses was that drug concentrations for missing years were the same as for years with data, given that there was little variation in drug concentrations from 2012 to 2014. Antiparasitics were not administered in Washington during the range of years with available data, and information on production or drug use during freshwater life stage was not available. Production data were not available from 2003 to 2010 in Washington; we instead subtracted Maine Atlantic salmon production (Maine Department of Marine Resources, n.d.) from U.S. Atlantic salmon production (NOAA, 2017) to estimate Washington production, since there are only two states with significant Atlantic salmon production. We estimated 2011 Washington production by averaging 2010 and 2012 production.

2.1.2. Maine, U.S

In Maine, Atlantic salmon are produced at nine sites located in four regions interspersed among small coastal islands and bays (Fig. 1). The four regions are Cobscook Bay on the U.S.-Canadian border, Eastern Bay, Machias Bay, and Swans Island. Three sites in Cobscook Bay are located 1200–4100 m from each other, the four sites in Machias Bay are located 300 m from each other with one site over a kilometer away, three sites near Swans Island are located 300 to 9700 m from each other, and three sites in Eastern Bay are 1000 to 1700 m from each other. A total of 193 net pens are available for production in Maine (Table A.2). Sites had between 5 and 21 circular pens arranged in a grid.

Maine data were provided by the Department of Marine Resources (DMR) and the Department of Environmental Protection (DEP). DMR maintains the Maine Aquaculture Map, an online mapping tool that provides basic information about aquaculture leases and licenses (Maine Department of Marine Resources, 2018). Atlantic salmon production from 1989 to 2010, and veterinary drug use from 2001 to 2008 were available on the DEP website (Maine Department of Marine Resources, 2009, n.d.). Data were provided by the agency via personal request for monthly fish counts, monthly average fish weight, and monthly veterinary drug use (antimicrobials and antiparasitics), treatment concentration, duration of use (in days), reason for application, and application method (bath, medicated feed) from 2014 to 2017. Data were provided at the pen-level, and aggregated up to site-level data because we observed that when veterinary drugs were administered they were given to all pens on a site. The database we analyzed is available in the Appendix.

Biomass was calculated by multiplying the fish count by the average fish weight. Production data were not available from 2012 to 2017; we instead subtracted Washington Atlantic salmon production from U.S. Atlantic salmon production to create an estimate for Maine (FUS 2016). We estimated 2011 Maine production by averaging 2010 and 2012 production. We averaged U.S. Atlantic salmon production from 2013 to 2015 as a proxy for production in years without data (2016 and 2017).

2.1.3. U.S. livestock and poultry

We compiled data on U.S. beef, pork, broiler chicken, and turkey production and antimicrobial use, and compared these data to Atlantic salmon. U.S. livestock production was accessed via the U.S. Department of Agriculture (USDA) (USDA, 2017). Antimicrobial sales by the pharmaceutical industry to livestock and poultry producers were reported by the U.S. Food and Drug Administration (FDA) (FDA, 2018) as required by the Animal Drug User Fee Act. In 2016, FDA began reporting sales of drugs by species for cattle, hogs, chickens, turkey, and an "other" category, which includes non-food animals (e.g., pets, horses), other minor species (e.g., quail), aquaculture, and other unknown uses. We developed species-specific antimicrobial use rate estimates by dividing antimicrobial sales by production (see Table A.4 and (FDA, 2003)).

2.2. International salmon aquaculture

Atlantic salmon production and antimicrobial use data were collected from multiple sources in March 2018. We reviewed farmed salmon reports produced by the Monterey Bay Seafood Watch program (Seafood Watch, 2018), and used these reports and online searches in Google Scholar to identify primary source material. Norway and Chile produce comprehensive reports on salmon production and veterinary drug use. In Norway, open statistics for fish production in aquaculture have been made since 1971 (Fiskeridirektoratet, n.d.), and statistics for drug consumption in aquaculture have been available since the mid-1980s (Bangen et al., 1994; Norwegian Institute for Public Health, n.d.; Simonsen et al., 2016). In Chile, salmonid production and drug use data are available in reports from 2005 to 2017 (SERNAPESCA, 2018). In Canada, annual antimicrobial use was reported by the British Columbian salmon industry from 1995 to 2015 (BCSFA, 2016), by industry scientists from 2003 to 2011 (Morrison and Saksida, 2013), and breakouts of specific drugs were reported by the British Columbia Ministry of Agriculture as personal communication to Seafood Watch (Seafood Watch, 2017a). Data from Atlantic Canada were less robust; production data were compiled from multiple sources by Seafood Watch (Seafood Watch, 2016) and antimicrobial use data were provided by the industry for 2012 to 2015; however, these data were provided for the entire Atlantic North America (including Maine) (Seafood Watch, 2016). We therefore subtracted our Maine antimicrobial use data from Atlantic North America to estimate antimicrobial use in Atlantic Canada. The Scottish Environmental Protection Agency provided antimicrobial use data for 2006 to 2016 as personal communication to Seafood Watch (Seafood Watch, 2017b), which we digitized using GraphClick (v. 3.0.3, Arizona). Scottish salmon production was calculated by the Scottish government (Munro and Wallace, 2017). For countries where multiple salmonids are produced in marine waters, we combined them.

2.3. Software

Data were stored and analyzed in Excel and graphed in Prism (v.7, GraphPad, La Jolla, CA). Maps of salmon aquaculture facilities were made using ArcGIS (ESRI, Redlands, CA).

3. Results

3.1. Washington Atlantic salmon production and antimicrobial use

Fig. 2 presents Atlantic salmon biomass and antimicrobial use on a monthly basis over a six-year period at eight production sites (a total of 21 production cycles). The grow-out periods were slightly less than two years, and pens were restocked after two to four months of fallowing. Actual production volumes were similar to NPDES permitted production volumes (Table A.1). The average feed conversion ratio was 1.5 ± 0.4 for the nearly thirty grow-out periods. There was no correlation between FCR and drug use in a production cycle. (Fig. A.5 presents additional production and antimicrobial use data from January 2018 to Septeember 2019.)

Antimicrobial drugs (florfenicol, sulfadimethoxine and ormetoprim in a 5:1 mixture, and oxytetracycline) were administered as medicated feed for disease treatment (Table 1). Antimicrobials were used in 93% (26 of 28) of production cycles (Fig. 2). Disease events are visible as clusters of months with antimicrobial use (Fig. 2). Florfenicol or sulfadimethoxine/ormetoprim was regularly administered after fish were stocked into pens, including some months when both florfenicol and sulfadimethoxine/ormetoprim were used. Sulfadimethoxine/ormetoprim was used more often in summer months and oxytetracycline in summer and fall, while florfenicol did not appear to have seasonal usage patterns (Fig. A.1).

Florfenicol, sulfadimethoxine/ormetoprim, and oxytetracycline were reported in NPDES permitting documents to be administered at doses of 10, 50 and 75 mg/kg fish, respectively for a 10-day duration (florfenicol and oxytetracycline) or a 5-day duration (sulfadimethoxine/ormetoprim) (Table 1).

3.2. Maine Atlantic salmon production, antimicrobial use, and antiparasitic use

Fig. 3 presents Atlantic salmon biomass and veterinary drug use on a monthly basis over a 4-year period from 2014 to 2017 at thirteen sites (a total of 17 production cycles). The grow-out periods were 20 to 28 months, and pens were restocked after a period of fallowing of five to 12 months. Oxytetracycline is the only antimicrobial used in Maine, which is administered as a medicated feed to treat bacterial kidney disease (BKD) (Table 1). Before an antimicrobial is used, Maine farmers identify the pathogen, perform sensitivity testing, and post a public notice that antimicrobials are in use (Sebastian Belle, Personal Communication). From 2014 to 2017 oxytetracycline was used in 24% (5/21) of production cycles, and additional data was provided for earlier years by Sebastian Belle (Personal Communication) indicating that 8% (13/166) of production cycles from 2003 to 2017 used oxytetracycline.

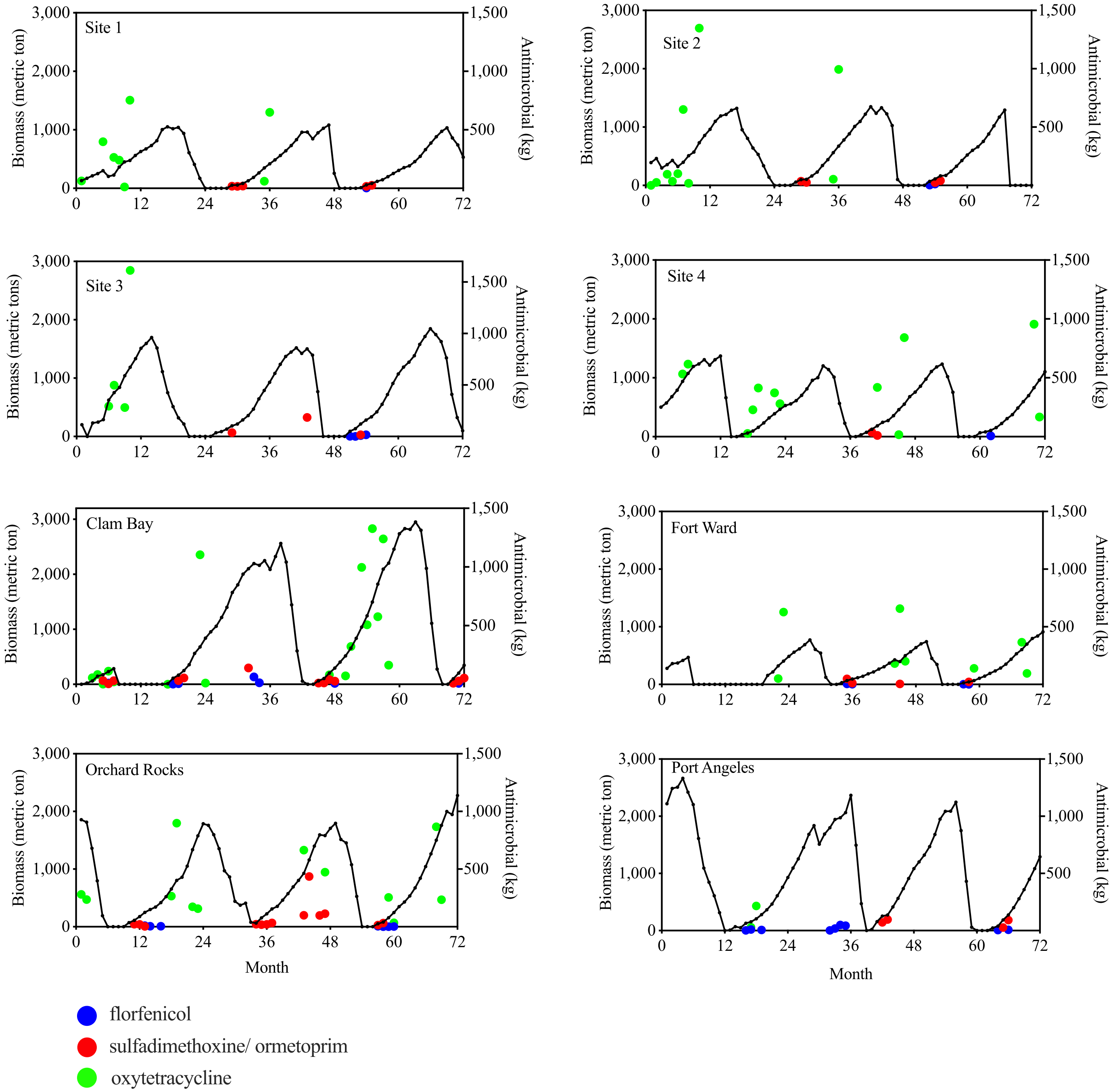

Fig. 2. Washington, United States Atlantic salmon monthly biomass (metric tons, black lines left y-axis) and monthly antimicrobial use (kg, colored circles, right y-axis) at eight sites from January 2012 (month 0) to December 2017 (month 72). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

There was a seasonal pattern in drug use from 2014 to 2017, with higher use during summer months (Fig. 2A). The reported duration of treatment was 8 days (st dev: 4 days; range: 2–15 days) and the dosage rate was 70 ± 15 mg/kg fish/day (Table 1).

Sea lice was treated with a medicated feed containing emamectin benzoate (SLICE®) and then a subsequent treatment with a hydrogen peroxide bath, but not as a combined treatment (Table 1). Similar to antimicrobials, pathogen identification and sensitivity testing are performed before antiparasitics are administered (Sebastian Belle, Personal Communication). Fish at Cobscook Bay and Machias Bay received more sea lice treatments than other sites. Emamectin benzoate was used in 62% of production cycles (13/21) from 2014 to 2017 with a total use of 4.5 kg (active ingredient). Additional data was provided for earlier years by Sebastian Belle (Personal Communication) showing that 28% (46/166) of production cycles from 2003 to 2017 used emamectin benzoate. The dosage was similar to the INAD approved dose of 0.05 mg/kg fish/day (US Fish and Wildlife Service, n.d.) and the average duration of use was 6 days (st dev: 3 days; range: 1–11 days) (Table 1). Hydrogen peroxide was administered in months following treatment with emamectin benzoate, at a concentration of 1200 to 1750 mg/l. No seasonal trends emerged regarding use of emamectin benzoate and hydrogen peroxide (Fig. A.2).

Table 1
Veterinary drugs used in Atlantic salmon production in Maine and Washington, United States.

Drug[a]	Application method	Dosage[b](mg/kg fish/d)	Duration (d)	Active ingredient (g/kg feed)[b,d]	Withdrawal period (d)	Diseases
Washington						
Florfenicol	Feed	10	10	0.66	15	Bacterial pathogens
Sulfadimethoxine - ormetoprim	Feed	50	5	5	n/a	Furunculosis, vibrio, myxobacterial and other bacterial pathogens
Oxytetracycline	Feed	75	10	11	n/a	Furunculosis, vibrio, myxobacterial and other bacterial pathogens
Maine						
Oxytetracycline	Feed	70 ± 15	8 ± 4	2.8–11.9	n/a	Bacterial kidney disease
Emamectin benzoate	Feed	0.044 ± 0.01	6 ± 3	0.0016–0.0056	60	Sea lice
50% hydrogen peroxide	Bath	1200–1750[c]	1	1200 - 1750	0	Sea lice
35% hydrogen peroxide	Bath	1750c	1	1750	0	Sea lice

[a] Common names for drugs: Aquaflor = florfenicol; Romet 30 = sulfadimethoxine-ormetoprim; Terramycin 200 = oxytetracycline; *SLICE* = Emamectin benzoate; Interox Paramove 50 = 50% hydrogen peroxide; Perox-Aid = 35% Hydrogen Peroxide.
[b] In Washington, proposed dosage is provided in the NPDES permit. In Maine, dosage was calculated based on reported drugs use and duration, number of fish per pen, and average fish weight. The calculated dosage in Maine was similar to the approved dosage.
[c] Reported in units (mg/l).
[d] Conversion to g/lb.: Aquaflor (0.3 g/lb); Romet-30 (2.27 g/lb); Terramycin 200 (5 g/lb. WA, 1.3–5.4 g/lb. ME).

3.3. Global salmon production and antimicrobial use

A total of 382,500 kg of antimicrobials were used globally in 2016 (Table 2), which is the most recent year with data from all producing regions. Florfenicol was the most often used drug (318,558 kg in 2016) and 80% of florfenicol use was in Chile. (Figs. A.3 and A.4 and Tables A.5 – A.7 provide production statistics, antimicrobial use, and antimicrobial use rates by region from 2003 to 2017). Over the most recent three-year period with complete data (2014 to 2016), the U.S. farmed salmon industry contributed 0.8% ± 0.1% annually to global farmed salmon production and administered 1.2% ± 0.6% of antimicrobials used in global salmon farming. Over the same time period, Norway and Chile accounted for 53% ± 3% and 35% ± 3% of global production and administered 0.06% ± 0.02% and 96% ± 0.09% of global salmon antimicrobials.

Fig. 4 presents antimicrobial use rates [e.g., total drugs used (mg) divided by total salmon produced (kg)] for major salmon producing countries. Norway, Scotland, British Columbia, and Maine have made significant progress towards reducing antimicrobial use, and Maine producers did not use antimicrobials from 2006 to 2011 or in 2017. Washington had the highest rate of antimicrobial use for 2012, 2013, and 2016. There were not enough available data on salmon production in Atlantic Canada to determine trends; however, total antimicrobial usage has dropped from 2013 to 2016 (Fig. A.3).

Table A.3 compares antimicrobial drug use rates by country from 2003 to 2017. We observed that reductions in use of certain antimicrobials and increases in others have occurred simultaneously. For example, in British Columbia there was a decrease in oxytetracycline and sulfadiazine/trimethoprim use over the past decade, and a concurrent increase in florfenicol. The Chilean industry reduced usage of oxolinic acid and flumequine and also had concurrent increases in florfenicol. Reductions in Scotland were largely through decreased use of oxytetracyline.

3.4. Comparing U.S. livestock and Atlantic salmon production and antimicrobial use

A total of 13,639 metric tons of antimicrobials were used by U.S. food animals in 2016 (Table 3). Cattle, hog, poultry, and turkey used 49%, 26%, 16%, and 8% of antimicrobials available for food animals. U.S. Atlantic salmon used 0.057% of all food animal drugs and account for 0.031% of U.S. food animal production by weight.

Roughly 8000 metric tons of medically important drugs were sold for use in U.S. food animals in 2016. (The term "medically important" is defined by the U.S. Food and Drug Administration as drug classes that have importance in human medicine (FDA, 2003)). Cattle, hog, turkey, and poultry used 45%, 39%, 9%, and 6% of medically important drugs available for food animals. U.S. Atlantic salmon used 0.098% of these medically important drugs. Tetracyclines were the most used class of medically important drugs in all animals (Table A.4).

4. Discussion

4.1. Antimicrobial use and resistance

Antimicrobial resistance is a worldwide public health crisis where the overuse or misuse of antimicrobials in any setting—aquaculture, agriculture, or human medicine—can compromise the treatment of bacterial infections in animals and humans (Ferri et al., 2017). The significance of this crisis for human health cannot be overstated. Unsuccessful antimicrobial therapy in 2016 caused an estimated 700,000 global fatalities and could cause 10 million fatalities by 2050 (Review on Antimicrobial Resistance, 2016). Many of the antimicrobials used in aquaculture are from drug classes considered "critically important" or "highly important" for human medicine (FDA, 2003; WHO, 2017b) and have been found to select for antimicrobial resistant bacteria when used in aquaculture production (Cabello, 2006; Cabello et al., 2013; Sapkota et al., 2008; Watts et al., 2017). The degree to which salmon aquaculture contributes to global antimicrobial use is well established for the major salmon producing countries (Cabello et al., 2013; Miranda et al., 2018; SERNAPESCA, 2018; Smith et al., 2010). It is widely known that Norway, the largest salmon producing nation has almost completely stopped antimicrobial use, while Chile, the second largest salmon producing nation accounts for most of global salmon antimicrobials use. Antimicrobial use in U.S. salmon aquaculture, however, has not been compiled or reported previously until this study. Drug usage was higher in Washington than Maine, and antimicrobial use rates (total drugs used divided by total salmon produced) in Washington were higher than several other salmon producing regions.

Surveillance, monitoring, and reporting of antimicrobial use in food animal production is an important component of national antimicrobial resistance policies, as antimicrobial use is proportional to antimicrobial resistance (WHO, 2017a). Large data gaps exist for many aquaculture species (Henriksson et al., 2017). Farmed salmon producers report antimicrobial use, and from these reports we estimate that antimicrobial use in global salmon aquaculture is 398 tons (in 2016) and can be compared to the 13,631 tons of antimicrobials sold to the U.S. livestock and poultry industries (FDA, 2018) and to the estimated

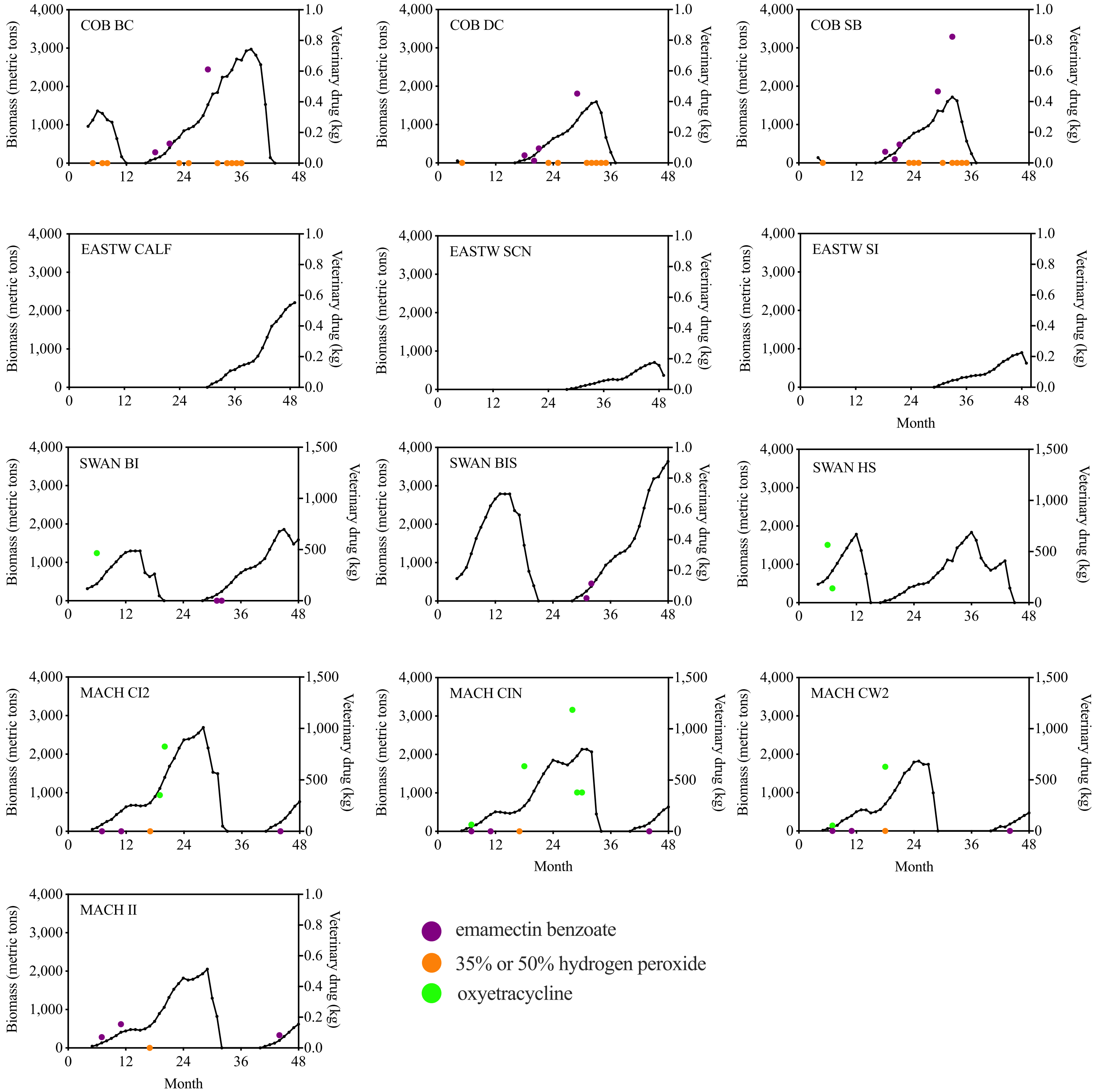

Fig. 3. Maine, United States Atlantic salmon monthly biomass (metric tons, black lines, left y-axis) and monthly veterinary drug use (kg, colored circles, right y-axis) at 13 sites from April 2014 (month 4) to December 2017 (month 48). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

63,000 tons of antimicrobials administered to terrestrial livestock globally (Van Boeckel et al., 2015). There are notable distinctions between antimicrobials used in aquaculture and terrestrial species and comparisons of antimicrobial use between livestock and fish need to be made with caution (Henriksson et al., 2015). Fish receive antimicrobials for therapy and not growth promotion (which were previously allowed for U.S. livestock), and drugs administered orally to fish via medicated feed raise different sets of issues than drugs administered orally to terrestrial animals due to the aquatic setting and biological differences.

One factor causing potentially increased consumption rates of antimicrobials in marine fish is that some drugs are known to have low bioavailability in seawater systems. Tetracyclines are prone to bind calcium and magnesium from seawater, and their absorption in fish is reduced (Lunestad and Goksøyr, 1990). These drugs enter the aquatic environment associated to organic material such as un-eaten medicated pellets and feces, and as a water-soluble fraction if eliminated via gills, feces and urine. It has been estimated that approximately 80% of the antimicrobials used in aquaculture enter the environment with their activity mostly intact (Cabello et al., 2013). While the water-soluble fraction is diluted in the surrounding water, much of the drug associated to organic material will settle on the seabed, bound to solid matter (feed, excreta, etc). The amount of drug reaching the sediment depends on the fraction of un-eaten pellets and the pharmacokinetic

Table 2
Salmon antimicrobial use (kg) by drug type and country, 2016.

Drug Class, drug	United States		Canada		Scotland	Norway	Chile
	ME	WA	Atl CA[a]	BC			
Macrolide							
Erythromycin	–	–	n/a	–	–	–	11,475
Amphenicol							
Florfenicol	–	57	n/a	2727	76	136	315,563
Quinolones							
Flumequine	–	–	–	–	–	–	11,475
Oxolinic acid	–	–	–	–	–	66	–
Tetracycline							
Oxytetracycline	1946	5634	n/a	2396	–	–	64,260
Potentiated sulfonamides							
Sulfadiazine/trimethoprim	–	–	n/a	–	–	–	–
Sulfadimethoxine/ormetoprim	–	194	–	95	–	–	–
Total	1946	5885	2343	5218	76	201	382,500

[a] Total antimicrobial use was available for Atlantic Canada, but not available by drug type. n/a = not available but reported in previous years (2012–2014).

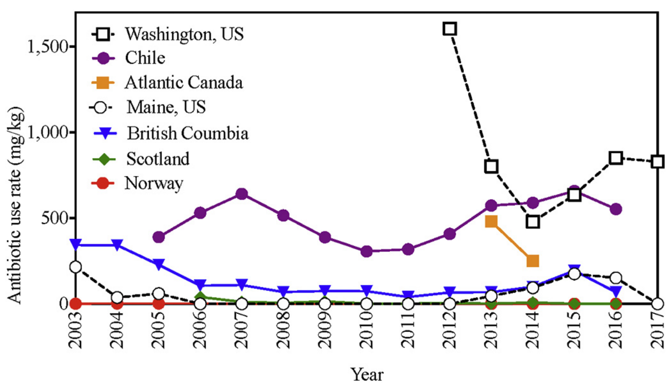

Fig. 4. Salmon aquaculture antimicrobial rates (mg/kg fish) by country or US state (2003–2017). Antimicrobial use rates (mg/kg) were calculated by dividing annual antimicrobial use by annual production (data provided in Tables A.5 – A.7). Data for Norway is based on all farmed fish species and Chile is based all salmonids (including Atlantic salmon, coho salmon, and rainbow trout). Salmon constitutes approximately 95% of the producting in Norway and Chile.

Table 3
United States animal production and antimicrobial use (metric tons), 2016.

Species[a]	Live weight	Antimicrobial use	Percent of antimicrobial use
Beef	18,222,708	6727	49%
Pork	15,600,494	3559	26%
Chicken	25,999,221	2209	16%
Turkey	3,434,154	1136	8%
Atlantic salmon, total	19,715	7.83	0.057%
Atlantic salmon, Washington	6917	5.89	0.043%
Atantic salmon, Maine	12,798	1.95	0.014%
Total	63,276,291	13,639	100%

[a] Salmon is compared to the top four U.S. food animal products. Livestock values based on sales of antimicrobial drugs and not actual usage. Antimicrobial drug use was not available for other species.

properties (absorption rate, metabolism and elimination pathway) of the drug in the fish. If the absorption and metabolism is low, most of the consumed drug will be eliminated as the parent compound via the liver and bile to the intestine and if readily associated with particles rich in organic content, the fecal particles may contain concentrations of the drug higher than the original pellets. Once reaching the sediment, factors like water solubility, affinity for organic particles, photo-stability and microbial and chemical degradation determine the persistence of the drug in the sediment (Lunestad et al., 1995; Samuelsen et al., 1994). Drugs are associated with small, slow sinking organic particles that may be transported a long distance before settlement (Buschmann et al., 2012; Capone et al., 1996). For example, in Norway, following medication with anti-sea lice agents at near shore cage operations, organic material collected one km away from the fish farm using sediment traps contained detectable drug residues (Samuelsen et al., 2015). Residues of oxolinic acid were found in wild fish, crustaceans, and bivalves near two marine salmon farms in western Norway that used this medication in feed (Samuelsen et al., 1992).

In addition, the use of antimicrobials in salmon farms could create hotspots for potential selection and generation of novel antimicrobial resistant bacteria and new assortments of antimicrobial resistance genes in the environment and in farmed fish (Cabello et al., 2016; Higuera-Llantén et al., 2018). Antimicrobial resistance genes could be taken up by mobile genetic structures including plasmids and integrative conjugative elements (ICEs), which can pass from one bacteria to another by horizontal gene transfer (Cabello et al., 2013). Antimicrobial residues, even at sub-inhibitory concentrations, can also stimulate mutagenesis, genetic recombination in integrons and horizontal gene transfer, increasing genetic variation fostering new antimicrobial resistance combinations (Friman et al., 2015; ter Kuile et al., 2016; You and Silbergeld, 2014). Moreover, use of antimicrobials in salmon aquaculture may facilitate the selection and capture by piscine and human pathogens of new antimicrobial resistance genes present in the yet unexplored marine resistome (Cabello et al., 2017; Fonseca et al., 2018). These concerns are not unique to salmon aquaculture, and exist for any food animal production system in which antimicrobials are used.

Antimicrobial drugs released from farms have been shown to select for antimicrobial resistance in environmental bacteria (Bravo, 2012), fish pathogens (Sørum, 2006), marine sediment (Buschmann et al., 2008; Shah et al., 2014), and possible human pathogenic bacteria (Aedo et al., 2014; Buschmann et al., 2012; Heuer et al., 2009). A study in Washington found drug residues and antimicrobial resistance in sediments near salmon aquaculture sites (Capone et al., 1996; Herwig et al., 1997). Human diseases caused by multi-resistant bacteria are infrequently linked to the consumption of seafood. An epidemiologic investigation in Ecuador found eating raw fish (not reported as farmed or wild caught) was associated with illnesses caused by multidrug resistant *Vibrio cholerae* (odds ratio: 10.0, confidence interval: 1.2–85.6) (Weber et al., 1994). Multidrug resistant and potentially pathogenic bacteria have been isolated in seafood from Brazil (Teophilo et al., 2002), India (Das et al., 2019), Nigeria (Igbinosa et al., 2019), the Philippines (Tendencia and de la Peña, 2001) and Thailand (Petersen and Dalsgaard, 2003). Researchers have detected several genetic elements conferring antimicrobial resistance to quinolones, tetracyclines, and βlactames that are shared between aquatic bacteria, fish pathogens, and human pathogens, and they appear to have originated in the aquatic environment (Cabello et al., 2013). Research has not adequately assessed whether antimicrobial use and resistance at salmon aquaculture farms could affect workers and residents living near farms, as previous research has shown for terrestrial animals (Casey et al., 2015; Hatcher et al., 2016).

4.2. Fish health and disease management

Diseases cost the global aquaculture industry $6 billion (U.S.) dollars each year (World Bank, 2014). The largest recent disease outbreak of ISA in salmon occurred in 2007 in Chile and cost the industry $2 billion and 20,000 jobs (World Bank, 2014). Even with enhanced biosecurity and optimized husbandry, the aquatic environment remains fertile ground for disease outbreaks associated with traditional or emerging pathogens, especially when hosts are exposed to inevitable stressors that occur throughout the fish production cycle.

Best management practices (BMPs) to prevent and control diseases in salmon net pen aquaculture have been summarized previously (Belle and Nash, 2009). BMPs include i) judicious site selection to ensure adequate water exchange; relative safety from extreme weather events, algal blooms, and/or concentrations of predators; and adequate water depth and sea bottom profile; ii) the use of high quality diets and effective methods for both feed dissemination and monitoring feed consumption; iii) rotation of rearing sites within a production area, including leaving individual sites empty (fallow) for specified periods; and iv) biosecurity BMPs including the adoption of an all-in, all-out population management plan (i.e., not mixing cohorts) and the avoidance of shared use of equipment (e.g., well boats) between production sites. Many of these BMPs go beyond what government regulators require, and instead are driven by corporate and industry-wide efforts. For example, an industry group, the Global Salmon Initiative (GSI), has a goal of having 100% of salmon farms operated by GSI members certified by the Aquaculture Stewardship Council by 2020 (Global Salmon Initiative, 2018). This is an example of market-driven aquaculture certification setting international standards, which can aid in enforcement and compliance using third party auditors (Henriksson et al., 2017; Jonell et al., 2013).

In addition to BMPs, general lessons from Norway regarding antimicrobial use could be applied to other countries. Norway has extensive experience in disease management as a means of controlling antimicrobial use. Substantial decreases have been seen in the use of antimicrobials in aquaculture since 1987 (Grave et al., 1999; Simonsen et al., 2013). The main reason for this is the application of effective vaccines added oil adjuvants against the main bacterial infective agents, along with additional factors such as zoning and farm siting to prevent horizontal transmission of infectious disease, using 'all-in-all-out' production systems, and mandating fallowing periods between year classes (Midtlyng et al., 2011; Sommerset et al., 2005). Norway and other producing countries continue to struggle with control of sea lice (Hjeltnes et al., 2017).

Another way of reducing disease pressure in aquaculture is by raising fish in relatively disease-free environments and using disease free brood lines. As growth in coastal production locations becomes constrained, there is increasing interest to implement land-based, closed containment production of Atlantic salmon, with the added benefit to potentially remove disease transfer between wild and farmed salmon (Summerfelt and Christianson, 2014). Through the use of specific pathogen-free eggs, biosecure groundwater, and effective biosecurity protocols and personnel management, the risk of obligate pathogen introduction can be minimized (Timmons and Ebeling, 2007). Disease associated with ubiquitous opportunistic pathogens, however, must always be considered regardless of rearing system type. Proper care must be taken to reduce stress due to the intensive, high-density environment, particularly since water is often recirculated, potentially allowing pathoges to proliferate to dangerous levels. Furthermore, intensive land-based production provides a novel environment for Atlantic salmon, and it is probable that novel diseases and/or pathologies will emerge as this industry sector continues to expand.

4.3. Antibiotics in U.S. aquaculture

There are a series of ongoing efforts by the U.S. FDA aimed at reforming antimicrobial use in U.S. food animal production. Recent FDA policies have: i) phased-out drugs for production purposes (i.e, growth promotion), however aquaculture does not use drugs for this purpose; ii) phased-out over-the-counter (OTC) drug sales; iii) decreased the use of medically important antimicrobials by 43% from 2015 to 2017; and iv) created veterinarian-client-patient relationships in which a veterinarian must issue a written statement (called a Veterinary Feed Directive (VFD)) in order to use VFD drugs (FDA, 2012, 2013, 2015, 2018). Several agencies in the federal government are monitoring drug sales and antimicrobial resistance in humans and meat to understand the significance of the issue for public health. These initiatives could impact the aquaculture industry in the following ways.

The first is the federal VFD rule that affects how aquaculture drugs are prescribed. Drugs previously sold OTC for extra-label uses (including oxytetracycline and sulfadimethoxine/ormetoprim used in salmon) became VFD drugs starting in January 1, 2017 (FDA, 2016). Our dataset ends December 2017, one year after the VFD went into effect, and it appears that high use of oxytetracycline in Washington may be related to the drug's OTC status. (Washington data from January 2018 to September 2019 is presented in Fig A.5 but not analyzed as part of this study). Sulfadimethoxine/ormetoprim was sold OTC in Washington as well; however, there are fish toxicity concerns with this drug which explains why the dose and duration of use rarely exceeded the extra-label use requirements. Florfenicol was under a VFD throughout this study and usage appeared to be consistent wtih the INAD label requirements. Future studies could assess what impact the VFD rule has on antimicrobial use in the aquaculture industry more broadly.

Reporting requirements are a second area where government policy could impact aquaculture. State regulators already collect data on salmon production to comply with NPDES permits, and Maine regulators also require salmon producers to provide a written request to use and discharge any new drugs, and post public notice that farms are using therapeutants. Regulators base their decision to approve or reject the request on whether the drug will have "significant adverse impacts on receiving water quality" (Personal communication, Maine Department of Environmental Protection). If net pen operations shift from state to offshore water would a federal agency provide a similar role in drug use reporting? Federal regulators who oversee offshore aquaculture could consider using Washington and Maine as models for reporting and public disclosure of monthly veterinary drug use at each farm site. Current federal antimicrobial reporting is done through the Animal Drug User Fee Act (ADUFA) in which the FDA reports sales of antimicrobials made by the pharmaceutical industry for use in select species (for cattle, pigs, chickens, and turkeys) (FDA, 2018). Annual ADUFA sales data are less relevant for public health measurements than monthly, farm-level drug use data. Additonally, ADUFA combines aquaculture with other groups of animals (including pets and horses), and future reports should consider break-out analyses for aquaculture, which would allow for better comparison to other food animal industries.

A third area is monitoring of drug residues and antimicrobial resistance at farms and in the food system. Maine and Washington regulators have the ability to request that the industry monitor the farm environment for drug residues or antimicrobial resistant bacteria, respectively, but have not done so recently (Maine DEP, Personal Communication). Regular monitoring is required, for example, in Maine for sulfides, which can trigger additional regular testing of benthic infauna. Our study findings suggest that routine monitoring of drug residues and antimicrobial resistant bacteria may be useful in Washington. It is in the best interest of the salmon industry, and for the health of the aquatic ecosystem, that its activities do not alter biodiversity and do not select for antimicrobial resistant bacteria, including piscine and human pathogens. Beyond the farm, several U.S. agencies work together to monitor antimicrobial resistance in humans and retail meats in a program called the National Antimicrobial Resistance Monitoring System (NARMS, 2015). This program samples retail livestock and poultry meat but excludes domestic aquaculture products, which should be added in the future.

There are several limitations to this study. There were some data gaps that required estimation, such as salmon production data for some years in Washington, Maine, and national data, also drug concentrations in Washington were estimated for some years based on other years with reported data. We reported Maine and Washington veterinary drug use on a monthly and annual basis, however, Maine data were provided on a more granular basis for some years. Data on veterinary drug use in freshwater life stages of salmon were not available for most countries including the U.S. The reason for drug administration (i.e., name of fish disease) was not provided with monthly data in Washington. Antimicrobial use in U.S. salmon was compared to antimicrobials sales data for U.S. livestock, which is not an ideal comparison because sales do not necessarily equate to use.

5. Conclusions

The U.S. net pen Atlantic salmon aquaculture industry is the first U.S. food animal industry we are aware that reports to the government with monthly antimicrobial use at the farm-level. Many of the antimicrobials used in aquaculture, including those in U.S. aquaculture, are from drug classes that are "critically important" or "highly important" for human medicine. Based on our data, the U.S. net pen Atlantic salmon industry is a minor contributor to antimicrobial drug use comparted to U.S. beef, pork, and poultry and Chilean salmon industries. There are relatively few approved drugs in the U.S. available to treat aquaculture diseases and more options are needed as well as continued work on vaccines. We anticipate that the VFD rule will further reduce antimicrobial usage by removing over-the-counter drug sales. Antimicrobials and antiparasitics used to treat farmed salmon diseases can select for resistance in target organisms. Tracking antimicrobial use in all types of food animal production is an important component of national and international antimicrobial resistance prevention policies.

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Author contributions

DL and JF conceived the study, designed the analysis, and collected the data. DL performed the analysis and led the paper writing. BL contributed data from Norway. JF, FC, CG, BL contributed to paper writing and editing.

Declaration of Competing Interest

The authors have no personal, financial, or professional conflicts of interest to report.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.aquaculture.2019.734820.

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