ANIMAL PATHOLOGY / REVIEW ARTICLE

DOI: 10.1590/1808-1657000362019

# Antimicrobials and resistant bacteria in global fish farming and the possible risk for public health

## *Antimicrobianos e bactérias resistentes na piscicultura global e o possível risco para a saúde pública*

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**ABSTRACT:** The use of antimicrobials in fish farming is a reflection of the fast aquaculture development worldwide. The intensification of aquaculture to achieve market demands could lead to an increase in infectious diseases by pathogenic bacteria. Consequently, antimicrobials act as controls for emerging infectious diseases, but their use must follow the rules and regulations of the country where the activity is performed. Although the regulations impose limits to the use of antimicrobials in fish farming, many studies show that resistant bacteria are isolated from this system. The selection of resistant bacteria is not limited only to the use of antimicrobials, but also to co-selection of resistance genes or even with cross-resistance processes. Resistant bacteria from fish farming are a serious concern because they can be acquired by humans with handling or food chain, which may represent a public health problem. In the present review, we present an overview of antimicrobials use in aquaculture, the antimicrobial resistance and the impact of antimicrobial and bacterial resistance from a public health perspective.

**KEYWORDS:** aquaculture; animal husbandry; fish production; antimicrobial resistance; food safety.

**RESUMO:** O uso de antimicrobianos na piscicultura é um reflexo do rápido desenvolvimento da aquicultura em todo o mundo. A intensificação da aquicultura para suprir as demandas do mercado pode levar ao aumento de doenças infecciosas por bactérias patogênicas. Consequentemente, os antimicrobianos atuam no controle de doenças infecciosas emergentes, mas seu uso deve seguir as regras e regulamentos do país onde a atividade é realizada. Embora os regulamentos imponham limites ao uso de antimicrobianos na piscicultura, muitos estudos mostram que bactérias resistentes são isoladas desse sistema. A seleção de bactérias resistentes não se limita apenas ao uso de antimicrobianos, mas também à cosseleção de genes de resistência ou mesmo por meio do processo de resistência cruzada. As bactérias resistentes da piscicultura são uma preocupação séria, uma vez que tais bactérias podem ser adquiridas pelos seres humanos no manuseio ou na cadeia alimentar, o que pode representar um problema de saúde pública. Nesta revisão, apresentamos uma visão geral do uso de antimicrobianos na aquicultura, a resistência antimicrobiana e o impacto da resistência antimicrobiana e bacteriana do ponto de vista da saúde pública.

**PALAVRAS-CHAVE:** aquicultura; criação animal; produção de peixe; resistência antimicrobiana; alimentos seguros.

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Received on: 05/13/2019. Accepted on: 06/21/2020

## INTRODUCTION

Global fish production is an activity that has been growing rapidly and is a major source of food for humans (HEUER et al., 2009; FAO, 2018). In 1961, the consumption of fish *per capita* in the world was 9.0 kg, which grew to 20.3 kg in 2016 (FAO, 2018), exceeding the 12 kg *per capita*/year rate suggested by the World Health Organization (WHO) (FLORES, 2013). This increase in consumption may be justified by the search for healthier eating habits: fish meat is a good alternative (CREPALDI et al., 2006).

According to FAO (2014), population growth, rising incomes and urbanization are factors that contribute to the increase in production. However, the possible emergence of bacterial diseases and the need to treat sick animals also increase (SHOEMAKER et al., 2000; MIRANDA et al., 2013). *Aeromonas* sp., *Vibrio* sp., *Streptococcus* sp., and *Edwardsiella tarda* are the mains pathogens that cause diseases in fish. These strains are responsible for different infectious diseases, such as skin lesions, abscesses, bleeding, and sepsis; these pathogens increase morbidity and mortality in fish and cause significant economic loss.

Thus, the use of antimicrobial drugs in the treatment and prevention of diseases was chosen as a method to solve this problem (OKACHA et al., 2018). The use of these drugs in aquaculture is important for successfully treating sick fish and maintaining the health and well-being of animals (MIRANDA et al., 2013). However, the use of these drugs must be carefully regulated and supervised. In past years, a great increase in the use of antimicrobials, especially on leading fish farms. In Vietnam, antimicrobial use in the production of pangasius catfish reached about 400,000 tonnes in 2010 (RICO et al., 2012). In Chilean salmon production, approximately 200,000 tonnes were used in 2000, doubling to 400,000 tonnes in 2007 (CABELLO et al., 2013).

This high numbers of antimicrobial agents in the production and in the aquatic environment play an important role in the selection of resistant bacteria. For CABELLO et al. (2016), the aquatic environment (freshwater and marine) can serve as both a reservoir of resistant bacteria and genes encoding antimicrobial resistance. The development and spread of resistant bacteria combined with the presence of antimicrobial residues in the environment represent dangerous risks to public health (ROMERO et al., 2012; DONE et al., 2015).

The dependence on these drugs shows how such actions must carried on with caution and can result in serious problems both in production (mortality and economic loss) and for humans' health. Thus, the present review aims to show the world's fish farming from the perspective of antibiotic use. Firstly, we discuss the use of antimicrobials licensed in world production; then, we present the main pathogenic bacteria found in fish production and its resistance profile to antimicrobial agents. Finally, we show how antimicrobial use and bacterial resistance could impact human health.

## Regulation on the use and distribution of antimicrobials in fish aquaculture

None of antimicrobial drugs used in bacterial infections are exclusively developed for aquaculture, although traditionally used in veterinary and human medicine. However, few antimicrobials are approved for use in aquaculture when compared to the greater number of drugs used for treatments of other animals, such as chicken. Information on the regulation and use of antimicrobials in aquaculture varies according to the country.

Why and how the applications of these drugs are performed in aquaculture? The increase in production and density of fish in farms causes diseases to emerge (SHOEMAKER et al., 2000). Just like in other types of animal production (cattle, pigs, and poultry), the aquaculture industry uses antibiotics to control bacterial diseases (ALDERMAN; HASTINGS, 1998; DEFOIRDT et al., 2011; DONE et al., 2015). Moreover, the regulation of antimicrobials in aquaculture is a factor that influences the range of agents accepted for use in each country (SMITH, 2008).

Therefore, there are three ways to administer antimicrobials in aquatic animals: incorporate the drug into the feed; into the water; or into injections (SMITH, 2008; HEUER et al., 2009). The method varies according to the health of fish in the tanks or depending on the purpose, such as infection prevention or rapid growth. Therapeutic use is applied to treat an established infection, whereas prophylactic use prevents the development of future infections (ROMERO et al., 2012). Some antimicrobials are also used as growth promoters, wherein low doses of antimicrobial agents are applied to increase the feed efficiency of animals and consequently increase weight gain. However, the use of antimicrobials for this purpose is questioned by the scientific community, because it can select resistant bacteria (MARSHALL; LEVY, 2011).

GUICHARD; LICEK (2006) identified oxytetracycline, first generation quinolones, sulphonamides, florfenicol, and amoxicillin present in products used in aquaculture in several European countries. However, in each country, no more than two or three antimicrobials are licensed for use in this type of activity. The limited availability of antimicrobial drugs for use in aquaculture is due to the establishment of Maximum Residue Limits (MRLs) proposed by the European Commission in 1990 (RODGERS; FURONES, 2009).

In Norway, the largest producer of salmon in the world, antimicrobial regulation is performed to control the volume and class of these agents in production. The country's implementation of a record was the result of several surveys indicating that the extensive use of antibiotics is not only harmful to aquaculture but also to the environment and human health. In addition to this control, the application of more hygienic management practices and the introduction of effective vaccines against infections contribute to the reduction in the use of antimicrobial drugs by the Norwegian industry (BURRIDGE et al., 2010).

In Chile, the second largest salmon producer in the world, the antimicrobials that are registered for use are: oxolinic acid, amoxicillin, erythromycin, flumequine, florfenicol, and oxytetracycline. However, farmers should report incidences of infections, which drugs were prescribed, as well as the posology and method of administration of those products to be able to use antibiotics (BURRIDGE et al., 2010). Unlike the Norwegian industry, Chilean aquaculture uses a large number of antimicrobials in the production of salmon. Scientific research conducted by SMITH (2008), which shows an estimated number of antimicrobials used by some countries, the author showed that Chilean aquaculture used 200 times more antimicrobials than the Norwegian production did (SMITH, 2008). This may be justified by the presence of specific pathogens, such as *Piscirickettsia salmonis*, which are common agents of disease in Chilean aquaculture, but do not cause problems in other countries, such as Norway (BURRIDGE et al., 2010).

In the United States, five drugs are approved by the Food and Drug Administration (FDA) for use in aquaculture, including four antimicrobials: oxytetracycline, florfenicol, sulfamiderazin, and sulfadimetozine combined with ormetoprim (BENBROOK, 2002; ROMERO et al., 2012). In Canada and Norway, the limitation of antimicrobial use is related to the application of vaccines (MINISTRY OF AGRICULTURE AND LANDS, 2009).

In Brazil, only florfenicol and oxytetracycline can be used to treat bacterial infections in aquaculture (PÁDUA et al., 2012), according to the norms of the National Programme for the Control of Residues and Contaminants (*Plano Nacional de Controle de Resíduos e Contaminantes* – PNCRC) by the Ministry of Agriculture, Livestock, and Supply (*Ministério da Agricultura, Pecuária e Abastecimento* – MAPA). This reduced regulation on antimicrobial agents for use in aquaculture is unfavorable, because it may lead producers to irregular use of other antimicrobial substances. HASHIMOTO et al. (2011) reports that many producers in Brazil use the malachite green dye as an alternative to antimicrobials. Although the dye has excellent results against a large number of microorganisms, it is also highly toxic to aquatic and terrestrial animals, and its application results in serious risks to human health, in both public and occupational perspective. In contrast, fluoroquinolones are promising, since they are approved in Brazil for use in other types of livestock (cattle, chicken, and pig) and are also approved in other countries, such as the European Union, Japan and China (QUESADA et al., 2013).

Many Asian countries rank among the production leaders in aquaculture. Consequently, scientific papers report a wide range of antimicrobials used in these countries. In a review published by RICO et al. (2012), approximately 36 different antimicrobials used in aquaculture in Asian countries were reported. These antibiotics belong to several classes, such as beta-lactams, tetracyclines, sulphonamides, aminoglycosides, macrolides, quinolones, nitrofurans, amphenicol, colistin, and even inhibitors, such as trimethoprim. This is a great concern considering that a wide range of antimicrobials is frequently used, such as colistin, a medicine commonly used in human medicine. Because it is a potent antibiotic, the use of colistin is restricted and can be toxic in high doses for humans. Nevertheless, with the increase in the prevalence of 'super'-resistant bacteria to other drugs, colistin has been introduced as a therapeutic option (POIREL et al., 2017). Obviously, just like with other drugs, the indiscriminate application of colistin in animal production may promote the emergence of super-resistant bacteria.

LIU et al. (2016) observed that the high frequency of resistance to colistin in humans in China is related to its intense use in animal production. The gene responsible for resistance to colistin (*mcr-1*) may have emerged in Chinese animal production due to the use of drug since the eighties (SHEN et al., 2016). Approximately 70% of China's production is for exports, which creates some concern regarding food safety (BROUGHTON; WALKER, 2010). The intensive and unnecessary use of antibiotics in fish farming interferes with the increase of bacterial resistance, which also damages production itself.

## Resistant bacteria in fish production

More than 100 bacterial species have been isolated from animals in aquaculture, but few of them have the potential to be pathogenic or significantly impact production (ALDERMAN; HASTINGS, 1998). However, both pathogenic and antimicrobial resistant bacteria are found in fish farming (GASTALHO et al., 2014), which are stimulated with the use of antibiotics to treat infections or as additives to promote growth (GAO et al., 2012). Pathogenic or aquatic bacteria may develop antimicrobial resistance when exposed to such drugs (ROMERO et al., 2012).

Nevertheless, bacterial resistance can also be promoted by co-selection or even by cross-resistance. According to SEILER; BERENDONK (2012), it is likely that the evolution of antimicrobial resistance and its spread was caused by anthropogenic pollutants, such as heavy metals. These metals can co-select mobile genetic elements that harbor genes that confer multiresistance (WELLINGTON et al., 2013). This shows us that more attention is needed to human actions and their role in the selection and dissemination of resistance genes. The persistence of fluoroquinolones in the environment may promote co-selection of extended-spectrum beta-lactamases (ESBL) genes, once that genes encoding resistance to both classes are often found in class 1 integrons (WELLINGTON et al., 2013). Certain antimicrobial drugs, even when applied only in the human medicine or veterinary medicine, may promote cross-resistance to several antimicrobials. Although its use is unique in veterinary medicine, enrofloxacin may promote cross-resistance to ciprofloxacin, which is used in cases of human medicine infections. In addition, cross-resistance may occur in antimicrobials of different classes, as observed in the case of oxolinic acid (quinolone), which may promote cross-resistance to oxytetracycline (tetracycline) (HOLMSTRÖM et al., 2003).

## Resistance profiles of main pathogenic bacteria isolated from fish

### *Aeromonas* spp.

The *Aeromonas* genus comprises a group of Gram-negative, facultative anaerobic bacteria, found in soil and water. Additionally, it can be associated to various infectious diseases found in animals and humans (IGBINOSA et al., 2012). *Aeromonas* is classified into two groups: mobile mesophilic with optimal growth between 35 and 37°C, associated to various diseases in humans; and psychrophilic, non-mobile, with optimal growth between 22 and 25°C, which can infect both fish and reptiles (MARTIN-CARNAHAN, 2005).

The main species associated to infections in fish are *Aeromonas hydrophila*, *A. sobria*, *A. salmonicida*, *A. veronii* (MAJUMDAR et al., 2006; IGBINOSA et al., 2012). The stress generated by inadequate management can generate a trigger for the appearance of infections caused by *Aeromonas* sp. in fish production (SAAVEDRA et al., 2004). Consequently, the use of antibiotics is the alternative for controlling the disease.

The antimicrobial resistance of *Aeromonas* sp. is widely identified. PENDERS; STOBBERINGH (2008) investigated the resistance profile of *Aeromonas* sp., isolated from catfish and eel created in closed systems in the Netherlands. A total of 79 isolates were submitted to antimicrobial susceptibility testing, in which resistance rates were observed for ampicillin (96%), oxytetracycline (65%), and trimethoprim (23%). SAAVEDRA et al. (2004) identified the presence of *A. hydrophila* isolated from rainbow trout in an experimental unit in Portugal. Certain strains showed high levels of resistance to beta-lactams antibiotics: amoxicillin (88%), ticarcillin (76%), ampicillin (65%), cephalothin (65%), and cefepime (54%). The authors also observed that some strains were resistant to imipenem (19%), an antimicrobial that belongs to the group of carbapenems used in human infections.

The intrinsic resistance of the *Aeromonas* genus to beta-lactams antibiotics is associated to a chromosomal beta-lactamase expression or an activation of efflux pumps (GASTALHO et al., 2014). Genes that confer resistance to a broad spectrum of beta-lactams antibiotics were identified in the genus. HENRIQUES et al. (2006) observed that 10.5% of *Aeromonas* sp., isolated from an estuary, possessed beta-lactamases genes, especially the gene $bla_{TEM}$. ESBL are encoded on mobile genetic elements, such as plasmids, transposons and integrons, which also harbour resistance genes to other classes of antimicrobials (PITOUT; LAUPLAND, 2008). Strains producing ESBL can hamper treatment and increase the morbidity of diseases associated to bacterial infections. CARVALHO et al. (2012) showed that 59% of untreated water isolates were resistant to at least two classes of antimicrobials. Furthermore, the presence of the *tet* gene encoding resistance to tetracycline in 10%, and the *bla* gene in approximately 29% of isolates was observed. The *tet* gene found in *Aeromonas* species is a result of strong anthropogenic pressure on aquaculture due to the use of antimicrobials, such as tetracycline (NAWAZ et al., 2006). In contrast, in Australia, although no antimicrobials are licensed for use in aquaculture, NDI; BARTON (2011) observed that 100% of *Aeromonas* strains isolated from fish present the *tet* gene. Although *Aeromonas* sp. presents typical characteristics of antimicrobial susceptibility, resistance profiles vary between studies because of the specific traits of the strains or selective pressure of the environment (JANDA; ABBOTT, 2010).

Another important factor in the resistance of *Aeromonas* sp. is linked to the activation of efflux pumps. The AheABC system, encoded by genes *Ahe*A, *Ahe*B, and *Ahe*C of *A. hydrophila,* is involved in the phenotype of multidrug resistance to cefuroxime, cefoperazone, erythromycin, lincomycin, pristinamycin, minocycline, trimethoprim, fusidic acid, and rifampin (HERNOULD et al., 2008).

### *Streptococcus* spp.

The genus *Streptococcus* belongs to the Streptococcaceae family and is Gram-positive cocci, which occurs in pairs or chains and has a diversity of species associated to infectious processes in humans (WHILEY; HARDIE, 2005). Six *Streptococcus* species are described as major pathogens in fish: *S. parauberis*, *S. agalactiae*, *S. iniae*, *S. dysgalactiae*, *S. phocae*, and *S. ictaluri*. Infections caused by *Streptococcus* sp. are called "estreptococosis" (FIGUEIREDO; LEAL, 2012).

ABDELSALAM et al. (2010) isolated *S. dysgalactiae* from sick fish in Japan, Taiwan, China, Malaysia, and Indonesia. The authors observed that 56% were resistant to oxytetracycline and harboured the *tet* gene. In Brazil, the antimicrobial susceptibility in strains of *S. agalactiae* isolated from Nile tilapia (FIGUEIREDO et al., 2006) was tested. The authors observed that the strains were resistant to nalidixic acid, gentamicin, and neomycin. This resistance profile can be related to selective pression due to previous contact with these antibiotics. Such data are interesting, because only florfenicol and oxytetracycline are licensed for use in Brazilian aquaculture, demonstrating the need for more accurate monitoring of both the use of antimicrobials in aquaculture and the contamination of water by residues from other animal farms.

### *Vibrio* spp.

The bacteria of *Vibrio* genus are Gram-negative curved rods, mobile due to the presence of a polar flagellum; they exhibit a fermentative metabolism. *Vibrio* sp. is associated to diseases in aquatic animals. *Vibrio anguillarum* is responsible for what is called "scarlet fever" in eels, but can infect other fish, causing necrosis in the abdominal muscles and erythema around the lid and inside the mouth (AUSTIN; AUSTIN, 2012). Some species, such as *V. parahaemolyticus* and *V. vulnificus,* may cause infections in both fish and humans (AUSTIN, 2010). *V. vulnificus* represents a public health problem, since it can be acquired in the food chain by consume of raw or undercooked fish (OLIVER, 2005).

GARCÍA-ALJARO et al. (2014), studying bacterial isolates of fish from various countries in Europe, identified approximate 20 species of the genus *Vibrio*, especially *V. anguillarum* (42%) and *V. vulnificus* (18%). The authors observed that the strains of *V. anguillarum* showed high rates of resistance to amikacin (89%), ampicillin (97%), aztreonam (44%), streptomycin (39%), and cefoxitin (87%).

### *Edwardsiella* sp.

The *Edwardsiella* genus, as well as *Escherichia*, belongs to the Enterobacteriaceae family. They are frequently isolated from infections of fish, such as catfish and eels, causing economic loss for many producers. Moreover, opportunistic pathogens are infrequently causing gastroenteritis in humans (SAKAZAKI, 2005). *Edwardsiella tarda* is responsible for systemic diseases in freshwater and marine fish worldwide and is called "edwardsiellosis" (MOHANTY; SAHOO, 2007; XU; ZHANG, 2014). Edwardsiellosis was identified in salmon, carp, tilapia, catfish, trout, and eels (MOHANTY; SAHOO, 2007).

JUN et al. (2004) investigated resistance determinants to tetracycline in *E. tarda* strains isolated from fish in South Korea. Each of the 20 isolates of *E. tarda* presented the resistance phenotype to tetracycline and contained one or two *tet* genes with 90% of these inserted into plasmids. These antimicrobials resistance determinants can be transmitted to human pathogenic bacteria. The strains of this study, in addition to tetracycline resistance, presented virulence. The authors warn that antimicrobial resistant bacteria in an aquaculture system can spread to fish, other animals and even humans.

### *Escherichia coli*

*E. coli* is a Gram-negative bacterium commonly found in the intestinal microbiota of humans and other endothermic animals, such as cattle, swine, and poultry (KAPER et al., 2004). Thus, it is widely used as an indicator of faecal contamination in food and environmental samples (CARSON et al., 2001). Although uniform, the microbiota of fish can be influenced by physical, chemical, and biological conditions of water where they live. Thus, even though *E. coli* does not belong to the fish microbiota, it can be found or isolated due to the contamination of the aquatic environment in which the fish is produced (BARBOSA et al., 2014).

RYU et al. (2012), investigating the presence of *E. coli* resistant to antimicrobials in fish samples from South Korea, observed that approximately 40% of the isolates were resistant to tetracycline, streptomycin, cephalothin, ampicillin, tircacilin, sulfamethoxazole/trimethoprim, and nalidixic acid. In this study, the authors observed that 41% of the isolates had class 1 integrons, containing genetic cassettes that encode resistance to the class of aminoglycosides and trimethoprim. JIANG et al. (2012) isolated 112 *E. coli* strains from commercialized fish in Guangzhou (China), with high rates of resistance to ampicillin, tetracycline, and florfenicol. Furthermore, 19% of these isolates contained genes encoding beta-lactamases, including TEM, SHV, and CTX-M. ROCHA et al. (2014) isolated 44 *E. coli* lines of tilapia marketed in Brazil, in which 25% were resistant to ampicillin, tetracycline, and sulfamethoxazole/trimethoprim.

Horizontal transfer of resistance genes facilitates the rapid spread of antibiotic resistance in bacteria. Multiresistance in strains of *E. coli* may be due to the presence of class 1, class 2, or class 3 integrons, or plasmids with multiple resistance genes (DENG et al., 2015). These plasmids frequently carry both antibiotic resistance and heavy metal resistance genes. The use of any of these compounds select the plasmid. This cross-selection contributed to the dissemination of multiresistant bacteria (CHOPRA; ROBERTS, 2001).

### *Weissella* sp.

Bacteria of the genus *Weissella* are Gram-positive with cells in the form of cocci or rods, not mobile, and live in variable habitats. Usually, bacteria of this genus are related to meat and vegetable products, or fermented beverages (BJÖRKROTH et al., 2005; BRUYNE et al., 2010). LIU et al. (2009) reported the first description of *Weissiela* sp. in fish farming.

FIGUEIREDO et al. (2012) investigated an outbreak of haemorrhagic septicemia in rainbow trout in Brazil, caused by *Weissella* sp. A total of 77 isolates showed a resistance profile to sulphonamide, erythromycin, oxytetracycline, and norfloxacin.

More intensive research on antimicrobial resistance in aquaculture is encouraged, given that the use of antimicrobials as growth promoters is still allowed in some parts of the world, such as in Brazil, where the use of florfenicol and oxytetracycline are not prohibited. The selection pressures due to the use of tetracyclines resulted in resistant bacteria. This resistance can be because of the presence of efflux proteins or ribosomal protection proteins. Both mechanisms can confer resistance to many other antimicrobials, like chloramphenicol, quinolones, erythromycin, beta-lactams, sulphonamides, and trimethoprim (CHOPRA; ROBERTS, 2001).

## Antibiotics used in fish farming: effects on public health

Antimicrobial resistance is a global concern of public health involving pathogenic and resistant bacteria (CAPITA; ALONSO-CALLEJA, 2013). The risks to public health related to the use of antimicrobials in aquaculture include the spread of resistant bacteria or resistance genes and the presence of residues of these agents in fish and the environment, which can be transferred to humans in the food chain (SMITH, 2008; OKACHA et al., 2018). In recent years, the concept of 'One Health', which prioritizes the health and welfare of humans, animals, and the environment, is gaining prominence worldwide (CAVALLI et al., 2015). This concept is being employed in the world aquaculture to minimize the risks to public health, animals and the environment (GOMAZ et al., 2014). The use of antimicrobials in aquaculture production and the zoonotic potential involving resistant pathogens and bacteria is of great importance for the triad from the One Health concept.

Many pathogens can affect humans in the consumption of raw or undercooked fish, or even by direct contact. In general, *Aeromonas* sp. are associated to gastroenteritis in healthy humans and can be fatal for immunocompromised individuals (TSAI et al., 2006). In less frequent cases, it can cause cellulitis, septicemia, hepatobiliary disease, meningitis, endocarditis, peritonitis, otitis, and osteomyelitis (VON GRAEVENITZ, 2007). In addition to consumption, another route of transmission of these strains is during contact with mucus or infected fish tissue, as well as wounds or cuts on people's hands are possible infection entries (LOWRY; SMITH, 2007). Strains of *V. vulnificus* can cause necrotizing fasciitis, edema, and swelling at the infection site. Data show that about 50% of patients with septicemia caused by *V. vulnificus* ingestion die (OLIVER, 2005; TANG et al., 2006). *V. parahaemolyticus* can cause acute gastroenteritis, which in many cases requires hospitalization, and may also progress to septicemia (NOVOTNY et al., 2004). Individuals infected by *E. tarda* may develop necrotic skin lesions, gastroenteritis, sepsis, and meningitis (MATSUSHIMA et al., 1996; NOVOTNY et al., 2004). Most infections by *S. iniae* occurs on an existent wound or injury caused by fish during handling, becoming an occupational health problem as well. Strains of *S. iniae* can cause cellulitis, systemic arthritis, endocarditis, and meningitis (WEINSTEIN et al., 1997; NOVOTNY et al., 2004).

The presence of these bacteria in fish highlights the zoonotic potential of these animals. Moreover, these strains can be pathogenic and exhibit resistance to antimicrobials, increasing the risks to human health. Antimicrobial resistance complicates or limits treatment options in human medicine. Thus, the use of these antimicrobial agents in production should be controlled (HEUER et al., 2009; REGITANO; LEAL, 2010).

The presence of antibiotic resistance genes in pathogenic bacteria suggests they may serve as reservoirs of these genes, which can possibly be transferred to humans. ISHIDA et al. (2010) monitored the incidence of multiple antimicrobial resistance genes present in Gram-negative bacteria, such as *Aeromonas* sp., *Vibrio* sp., and *E. coli*, isolated from fish in Egypt. A total of 33% of the samples tested had the phenotype of multidrug resistance, and 7% were positive for class 1 integrons with 12 genes from different cassettes. Genes that determine resistance to tetracyclines, quinolones, florfenicol and genes encoding ESBL were observed in these mobile genetic elements. Besides that, resistant bacteria in animal food represent a danger to public health, because resistance can be transferred to the host bacteria (ROMERO et al., 2012), just like resistance genes linked to plasmids can be transferred to strains of human microbiota. AEDO et al. (2014) observed that the gene for determination of quinolone resistance [aac (6 ')-Ib-cr] present in marine fish bacteria was also present in uropathogenic *E. coli* isolates (UPEC), suggesting that the gene can be found in bacteria from different environments.

## Occupational health and antibiotic resistance

Workers on aquaculture are at risk of exposure to super-bacteria and may carry these dangerous pathogens to their family and community (IUF, 2018). In addition to the risk they pose to themselves, workers may unknowingly act as 'carriers' of these pathogenic microbes and pass on the risks of disease to others. The contact of workers with antimicrobial resistant pathogens in aquaculture can occur during the handling of animals with resistant strains and/or the use of needles in the vaccination. The risk increases if workers have lacerations, cuts or wounds on their skin. As pointed out by IUF (2018), the exposure to the hazard is due to an unsafe and unsanitary working environment. For the most part, the health and safety of workers is ignored when considering AMR. Therefore, regulatory agencies must recognize antimicrobial resistance as a work-related disease as well.

Considering the hierarchy of controls, the first measure to be chosen should include complete restriction of the use of all classes of medically important antimicrobials in aquatic animals for the prevention of infectious diseases that have not yet been clinically diagnosed; or for growth promotion. Another important measure is not to use antimicrobials classified as highest priority for human medicine for the treatment of production animals. The second line of measures to be adopted includes use of quarantine and specific pathogen-free certified stocks, excluding vectors and external sources of contamination, and preventing internal cross-contamination. Therefore, if previous steps are not possible, administrative measures and use of personal protective equipment should be adopted. They include cleaning and disinfecting shoes, removing work clothes before leaving the farm, washing and drying hands, and not using electronic devices during animal activities.

# FINAL CONSIDERATIONS

Each country has its own regulations on antimicrobials used in fish production. We highlight several bacterial species of fish farming that contain resistance genes to important antimicrobials, representing a potential risk to public health. These data on resistance to multiple drugs imply the need to monitor the production chain.

The prudent use of antibiotics in aquaculture under veterinary supervision is essential to ensure the safety of aquaculture products. Good animal husbandry practices and the use of alternatives to antibiotics, such as vaccination and probiotics, are the recommended alternatives to reduce antimicrobial use and residues in aquaculture and its consequent effects (OKACHA et al., 2018). Moreover, adopting biosafety measures that prevent the entry of pathogens into farms or incubators is also important, thus reducing the risk of disease outbreaks and the consequent use of AM (BONDAD-REANTASO et al., 2012; HENRIKSSON et al., 2018).

**ACKNOWLEDGEMENTS:** Not applicable.

**FUNDING:** This work did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

**CONFLICTS OF INTEREST:** All authors declare that they have no conflict of interest.

**ETHICAL APPROVAL:** Not applicable.

**AVAILABILITY OF DATA AND MATERIAL:** Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

**AUTHORS' CONTRIBUTIONS:** Conceptualization: Brito, B.G.; Gazal, L.E.S. Writing – original draft: Gazal, L.E.S.; Brito, K.C.T.; Kobayashi, R.K.T.; Nakazato, G.; Cavalli, L.S.; Otutumi, L.K.; Brito, B.G. Writing – review & editing: Gazal, L.E.S.; Brito, K.C.T.

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