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Gram-negative bacterial diseases in cold-water aquaculture: Pathogens, impacts, and control strategies—A comprehensive review

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Abstract
The most rapidly expanding food production sector on a global scale and is currently a significant portion of the world fish consumption, aquaculture is central to the economies and nutrition of the world, where the salmon and trout in cold water economies are key players. Concurrently, the upgrading of cold-water aquaculture has led to a favourable disease outbreak environment specifically due to the high stocking density, the environmental stressor and the poor quality of water. Essentially causing major systemic diseases; bacterial cold-water disease, furunculosis, enteric red mouth disease and vibriosis resulting in severe mortality, tissue damage and immense economic losses in farmed salmonids are the gram-negative pathogens particularly *Flavobacterium psychrophilum, Aeromonas salmonicida, Yersinia ruckeri and Vibrio anguillarum.* The routes of vertical and horizontal transmission, the presence of carrier fish and environmental reservoirs and increased antimicrobial resistance due to the extensive use of antibiotics also contribute to these infections. The level of efficiency may be varied depending on the control strategies such as Vaccination, better husbandry, chemotherapeutic agents' application, probiotics and immunostimulants. With which this disease has been controlled worldwide that is a completely differ from just introducing the vaccines only especially in early life stages but understanding on pathogen-host environment interactions and deficiency of available vaccines so far particularly in early stage are being remained challenging to standing against better disease control. The biosecurity level therefore needs to be strengthened in addition to enhancing environmental and nutritional standards, introducing strategies of reduction of stocking densities in and developing a more specific prophylactic system which is easily utilized to protect fish health, enhance productivity and subsequent sustainability of the cold -water aquaculture.

Keywords: Aquaculture, cold-water fish, salmonids, gram-negative bacteria, antimicrobial resistance, probiotics, vaccination, sustainable aquaculture

Introduction

Aquaculture is recognized as the most rapidly expanding sector of global food production. It fulfils approximately one-third of the global dietary requirements, thereby playing an indispensable role in the preservation of international food security (Ravi *et al*., 2007) [35]. By 2022, it accounted for 50.9% of total fish production globally. On the other hand, aquaculture is in the development, and it is predicted to reach 93.7 million tons, there will be increase in consumption of farmed aquatic products. Cold water fish (CWF) species, such as salmon and trout are good for the economy, good for health, and for that reason crucial to the aquaculture business. The population of the Asia-Pacific region is rapidly increasing, and more people are living better lives, which means that more food is being produced. According to De Bruijn *et al*. (2018) [9], the sector of the region is predicted to increase by about 30% in 2030 and is predicted to reach 93.6 million tons. Overall, aquaculture is still considered to be one of the fastest growing areas of the food production on the world. Commercial and industrial aquaculture has only been on the rise, and it is a prominence that is growing, fast and substantial for the past 20 years to 30 (Verdegem *et al*., 2023) [45]. The state of world Fisheries and Aquaculture 2024 finds that in 2022, the global fishery and aquaculture production was 223.2 million tonnes, which is 4.4% more than 2020. This was noted by Kobayashi *et al*. (2015) [24] cold-water fish (CWF) species, including salmon and trout, are crucial to the aquaculture business since they are good for the economy and are also beneficial for health.

The risk of infectious illnesses has increased as aquaculture has expanded and intensified. Fish that are kept in high density are more likely to get sick because they don't have enough space, sick fish aren't pulled out of the water soon, they don't get the correct nutrition, and they must go through stressful handling procedures (Kim, 2013) [22].

However, fish are also exposed to hundreds of bacterial pathogens, and these cause horrific diseases that result in the losses of billions of dollars per year throughout the entire world Besides impairing the health of fish, these outbreaks reduce yields in production and cause the long-term sustainability of aquaculture to reduce. Diseases spread rapidly due to overcrowded conditions during rearing, which in most cases leads to extensive epidemics and significant financial losses (Rohani *et al*., 2022) [36]. The culture of cold-water fish is a reliable and cheap source of high-protein food to sustain global food security. As the world's population rises and the number of wild-caught fish stays the same, this type of aquaculture has grown more essential, especially in poorer nations (Beijer Institute, 2022; Pradeep Kiran, 2019; FAO, 2024) [4, 11].

Aquaculture gives millions of people throughout the world food security and jobs. It employs more than 20 million people full-time, part-time, or on a temporary basis (Hendam *et al*., 2023) [14]. Fish's immune systems are significantly weaker in cold water systems since the water is cold and not very clean. This makes it easier for them to obtain bacterial infections. The increasing growth of fish farms has made it easier for the disease to spread.

There is need to know the different circumstances that influence development and promote the transmission of infection (Duman *et al*., 2023) [10]. These are acute bacterial diseases that affect salmon and trout like Vibriosis, Furunculosis and Bacterial kidney disease (BKD), that cause enormous losses of hundreds of millions of dollars annually in terms of high mortality and defensive health of fish. Within the recent decades, the rise of fish rearing activities has only increased and intensified bacterial infection in salmonids and other cold-water species. Over the past few decades, the growth of aquaculture methods has made bacterial infections more common and worse, especially in salmonids and other cold-water species (Lillehaug *et al*., 2003) [26].

Septicaemia, tissue damage, and dermal lesions are the main pathological outcomes of aquatic organisms caused by bacterial pathogens as the major etiological agents of diseases in aquaculture (Bethke *et al*., 2011).

Diseases spread considerably faster when there are a lot of fish and live fish are moved between farms without sufficient health inspections. Bacterial diseases in cold-water aquaculture remain a critical concern, stemming from a lack of understanding of pathogen-host-environment interactions and the ineffectiveness of control measures despite extensive research initiatives

Gram-Negative Bacteria

The cell wall of Gram-negative bacteria is distinctive, featuring a thin peptidoglycan layer situated between the cytoplasmic (inner) membrane and an outer membrane rich in lipopolysaccharides. Consequently, these bacteria appear pink or red in Gram staining, as their structure prevents effective retention of the crystal violet dye, unlike Gram-positive bacteria. The outer layer is a protective layer that is also loaded with endotoxins and may result in extreme immune responses in their hosts (Erridge *et al*., 2002; Silhavy *et al*., 2010) [54]

Bacterial infestation

New research has discovered several new forms of bacteria that can make fish sick in cold water. Aquaculture Rainbow trout (Oncorhynchus mykiss) is a big part of the aquaculture business because it is easy to farm, can live in many various places, and can adapt to new conditions. The eggs hatch in approximately a month, and the fry can be weaned in one to three months after that, which is a significant advantage (Henryson *et al*., 2005). Some Gram-negative bacteria, like Pseudomonas, Edwardsiella, Aeromonas, Flavobacterium, and Vibrio, are the most important pathogens that cause furunculosis, despite current worldwide success.

Such bacterial infections might lead to high mortality rates in specific situations when the conditions are stressed like low temperature and poor-quality water that are the primary factors that significantly impact the health of fish and result in economic losses through mortality and poor productivity (Pekala-Safinska *et al*., 2018).

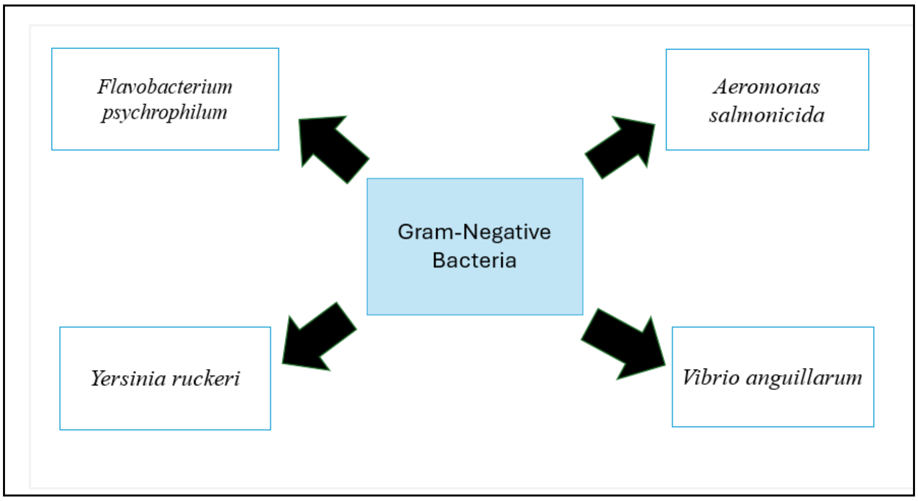

Fig 1: Schematic illustration depicting notable Gram-negative bacteria responsible for bacterial pathologies in cold-water aquaculture

Major gram-negative pathogens in cold-water systems:

- ***Flavobacterium psychrophilum***

Flavobacterium psychrophilum is a rod-shaped (3-5mm), Gram-negative bacterium and from the phylum Bacteroidota. It is the causative agent of bacterial cold-water disease (BCWD) and rainbow trout fry syndrome (RTFS), which cause substantial mortalities and economic losses in farmed and hatchery raised salmonids (family Salmonidae) around the world (Loch & Faisal, 2017) [27].

The bacterium was first described during an outbreak of mortality in freshwater salmon in 1948 and has since been found to be present in freshwater environments, which is a problem for aquaculture (Starliper, 2011) [39]. This pathogen is recognized as a major salmonid pathogen around the world with potential for causing mass mortalities, and economic loss in farm and hatchery environments especially cold-water salmonids like rainbow trout (Oncorhynchus mykiss) and Atlantic salmon (Salmo salar) (FAO, 2020).

Fish have been recognized as excreting significant volumes of microorganisms. Previously, BCWD was thought to be a part of other groups of bacteria, such as Cytophaga psychrophila and Flexibacter psychrophilum (Bernardet *et al*., 1996) [5]. *Flavobacterium psychrophilum* was associated with bacterial cold-water illness, which emerged as a significant health threat and a challenge for aquaculture. It usually affects juvenile fish, but it can also get into smolts and yearlings. When the water is less than **12 °C**, it is normally in the form of outbreaks and horizontal transmission is mainly caused by dead fish (Vatsos *et al*., 2001).

It causes BCWD and Rainbow Trout Fry Syndrome (RTFS), which kills a lot of young fish (Nematollahi *et al*., 2003) [31].

Flavobacterium psychrophilum spreads both horizontally and vertically. When sick fish give birth, they release a lot of bacteria into the water, which is then transmitted either by direct contact or indirectly by the water, especially in overcrowded farms.

Flavobacterium columnare (columnaris illness), *Flavobacterium branchiophilum* (bacterial gill disease), and *Flavobacterium psychrophilum* (cold-water disease) are the three primary forms of Flavobacterium that cause the most serious bacterial diseases in freshwater (Ilardi *et al*., 2009) [17].

- ***Aeromonas salmonicida***

The longest-known fish pathogen is *Aeromonas salmonicida* which grows successfully in freshwater and saltwater in all parts of the world. Aeromonas is classified as a Gram-negative, oxidase-positive, and facultatively anaerobic rod-shaped bacterium (Martínez-Murcia *et al*., 2016) [28].

The subspecies Salmonicida is responsible for inducing furunculosis, a systemic disease in salmonids that poses a significant risk of mortality to both wild and aquaculture salmon in freshwater and marine environments (Wang *et al*., 2020) [47].

It was first discovered in German hatcheries in 1890, and initially, it was believed to occur only in salmonids produced on a large scale. This disease represents a critical concern within the area of salmonid aquaculture (Austin and Austin, 1987) [1].

Aeromonas salmonicida exhibits a non-motile characteristic and demonstrates a preference for lower temperature environments, with optimal growth conditions occurring between 22 and 25°C. This pathogen has the capacity to infect both wild and cultivated fish, with a prominent association with the occurrence of furunculosis. The genus comprises 26 distinct species, each exhibiting varying degrees of motility and preferences for temperature (Aravena-Roman *et al*., 2012) [56].

Transmission of the bacteria is mainly through direct contact with fish or infected water. The discharged bacteria of sick or diseased fish could be left to live in the water to facilitate the spread through skin abrasives and mucosal surfaces. The incidence and severity of infections are heightened under conditions of reduced oxygen availability and elevated temperatures. Individuals that survive the infection may act as carriers, harboring the bacteria for extended periods, thereby facilitating the dissemination of the infection within aquaculture settings.

- ***Yersinia ruckeri***

Yersinia ruckeri is identified as a facultative anaerobic, rod-shaped, and Gram-negative bacterium that is a member of the Enterobacteriaceae family. This pathogenic species has the capacity to infect a range of hosts, including both animals and humans, with fish being a notable target. In the 1950s, *Yersinia ruckeri* was first found in rainbow trout, Oncorhynchus mykiss (Walbaum), in the Hagerman Valley of Idaho, USA (Rucker 1966) [38].

It is now common in fish populations in North America, Australia, South Africa, and Europe. Enteric red-mouth disease (ERM) is caused by a bacterium that resides in salmonids all over the world. However, it is more common in areas where trout and salmon are farmed a lot. Also known as ERM, that results in economic losses to all ages.

It was initially detected in Idaho in the 1950s (Ross *et al*., 1966) [37], and in older fishes, chronic manifestations are mainly observed.

The diseases can be insignificantly mortal at an early stage, but this can accumulate over time resulting in huge losses on stocks.

It spreads through physical contact, and 25% of rainbow trout can carry the *Yersinia ruckeri* when the body is under stress, it releases ruckeri bacteria from the lower intestine. Gills are a highly significant point of entry and then disseminate throughout the body (Tobback *et al*., 2009) [42].

ERM is a short-term sickness in tiny fish, but it can endure a long time in bigger fish. As much as these bacteria can be found in other species, salmonids are especially vulnerable to these bacteria, notably rainbow trout. After being excreted, bacteria can live in water, sediments, and biofilms for months.

- ***Vibrio anguillarum***

This pathogenic bacterial infection is referred to as vibriosis, boil disease, saltwater furunculosis, or ulcer disease (Kubota and Takakuwa 1963) [25]. The pathogenic species responsible for vibriosis is *Vibrio anguillarum*. V. salmonoids represent the predominant species associated with cold-water vibriosis or Hitra illness. Water is the most prevalent route that cold-water vibriosis spreads, and it can be seen at temperatures below 10°C. Trout that live in salt water are more likely to have the halophilia Vibrio species, which can spread quickly and kill a lot of fishes which can have economic impacts (Ina-Salwany *et al*., 2019) [18].

Vibrionaceae is one of the most prominent and well-known members of the family. It causes haemorrhagic septicaemia in both cold- and warm-water fish, like Atlantic salmon and rainbow trout.

Frans *et al*. (2011) [13] say that it spreads from one fish to another, especially in farms that are extremely crowded. Environmental stressors, including temperature variations and handling stress, are associated with degraded water quality and may cause stress in organisms.

Table 1: Major bacterial diseases affecting cold water fishes, their causative agents, host species, and clinical signs

Causative agent (genus / key species)	Common disease name(s)	Main fish species affected (cold-water aquaculture)	Typical environment (system, salinity, temperature)	Main clinical signs/symptoms	Example reference
Flavobacterium psychrophilum	Bacterial Coldwater disease (BCWD); Rainbow trout fry syndrome (RTFS)	Primarily salmonids: rainbow trout, Atlantic salmon, Coho salmon, char; fry and juveniles most susceptible.	Freshwater hatcheries and grow-out systems (raceways, tanks, RAS); cold water, typically 4–15 °C	Lethargy, darkening, fin and tail erosion, superficial skin ulcers/lesions, pale gills, exophthalmia; in fry, skeletal deformities and high cumulative mortality.	Gómez, E. *et al*., 2014 [50], Microbial Biotechnology, 7(5), 414–423.
Aeromonas salmonicida subsp. *salmonicida*	Furunculosis	Mainly salmonids: Atlantic salmon, rainbow trout, brown trout, char.	Mostly freshwater or low-salinity (brackish) hatcheries	Darkening, lethargy, haemorrhages in musculature and at fin	Van Vlierberghe, P. & Frey, J., 2013

(representing Aeromonas in cold-water salmonids)			and grow-out; cool water 8–18 °C, especially in intensive tank.	bases, deep subcutaneous abscesses (“furuncles”), abdominal distension, septicaemia, sudden high mortalities.	[52], Microbial Biotechnology, 6(2), 135–146.
Causative agent (genus / key species)	Common disease name(s)	Main fish species affected (cold-water aquaculture)	Typical environment (system, salinity, temperature)	Main clinical signs/symptoms	Example reference
Yersinia ruckeri (genus Yersinia)	Enteric red-mouth disease (ERM)	Primarily salmonids: rainbow trout, Atlantic salmon, Coho salmon and other farmed salmonids	Freshwater intensive systems (raceways, tanks, RAS); cool–moderate temperatures, commonly 10–18 °C	Haemorrhages in mouth, opercula and gill arches (“red-mouth”), exophthalmia, darkening, abdominal distension, enteritis, splenomegaly, variable but sometimes high mortality.	Fajardo, C. *et al*., 2022 [53], International Journal of Molecular Sciences, 23(22), 12949**.**
Vibrio spp. (e.g. *V. anguillarum)*	Vibriosis; cold-water vibriosis (“Hitra disease”)	Marine and euryhaline cold-water species: Atlantic salmon (sea stage), rainbow trout and other marine/cold-temperate fish	Marine and brackish cage/net-pen systems; cool coastal waters 4–18 °C (cold-water vibriosis outbreaks often at ≤10 °C)	Acute or subacute haemorrhagic septicaemia with skin and fin haemorrhages, petechiae at fin bases, ulcers, darkening, anorexia, rapid mortality in severe outbreaks	Hickey, M. & Lee, J., 2018 [51], Reviews in Aquaculture,10(3), 585–610.

Pathogenesis, Clinical Manifestation, Diagnosis, and Therapeutics

1. *Flavobacterium psychrophilum*

The microorganism responsible for bacterial cold-water disease is *Flavobacterium psychrophilum*. The clinical presentation of this condition includes the appearance of open lesions on the integument, irregular patches, and deteriorated fins, ultimately culminating in tissue necrosis. The first sign is that the adipose fin along the caudal peduncle turns white. The injured rainbow trout show too much mucus, pale gills, erosion of the caudal fin, and neutrophils getting into the muscle (Makesh *et al*., 2015) [57]. Other clinical indications include a large abdomen, severe anaemia, bilateral exophthalmia, and internal bleeding in more serious cases. The pathogen is often found in lamellar capillaries, the kidney, heart, and spleen, with little or no inflammation (Knupp, 2023) [23]. Histopathology usually shows localized necrosis in the spleen, liver, and kidney, as well as vacuolar degeneration and higher eosinophilia in renal tissues (Starliper, 2011) [39].

A wet mount inspection can show thin, long, flexible rods (0.5–1.0 × 4–10 µm), which might help to make a quick guess about the problem (Park *et al*., 2023) [33]. However, early lesions can be challenging to detect. Antiseptic and chemical baths are beneficial for fish. Skin infection at an early stage can be treated with the help of antiseptic baths. To stop its spread, fish shouldn't be kept in big groups, and diseased individuals should be removed. Immunofluorescence, immunohistochemistry, ELISA, and PCR are some of the most advanced approaches to find illness in fish (Vatsos *et al*., 2006) [44].

The other available alternative is antibiotics, which also tend to be resistant to the pathogens as time passes—this is the reason why antibiotic sensitivity testing is a mandatory requirement. Freshwater aquaculture species do not have any commercially available vaccines (Van Vliet *et al*., 2017) [43].

2. *Yersinia ruckeri*

Enteric red-mouth disease (ERM) is a disease caused by *Yersinia ruckeri* and mainly affects young fish, especially fingerlings. The smaller fish are more prone to infection, but the bigger fish are longer-term carriers. In the early stages of an outbreak, mortality tends to be low but under the circumstances when the quality of water is suboptimal or the environment experiences a high level of stress, it could grow considerably. Fish with ERM frequently move slower, consume less, have exophthalmia, and have obvious subcutaneous haemorrhages, especially around the mouth and neck (Horne and Barnes, 1999) [16].

Septicaemia and inflammation are predominantly identified histopathologically in the kidney, spleen, liver, heart, gills, and regions exhibiting petechial haemorrhages. Other indicators include petechial haemorrhages in muscles and organs, reddening of the lower intestine. Histopathology reveals systemic septicaemia and persistent inflammation in essential organs, characterized by significant alterations including hyperaemia and necrosis. The gills are a major route for *Y. ruckeri* to enter the body rapidly (Waine *et al*., 2023) [46].

Diagnosis employs culture techniques across many media, in conjunction with biochemical and serological tests, as well as molecular technologies like PCR to enhance sensitivity. Antibiotics are useful; however, pathogen is showing resistance. Formalin-killed, subunit, and live attenuated vaccinations provide protection; however, concerns regarding carries and environmental safety persist (Calvez *et al*., 2014) [7]

Probiotics and immunostimulants, including Bacillus and Carno bacterium spp., can enhance immune function and reduce disease (Kim & Austin 2006) [21].

3. *Aeromonas salmonicida*

A. salmonicida was widely regarded as the etiological agent of furunculosis in fish. Furunculosis, induced by *Aeromonas salmonicida*, and is characterized by acute or chronic haemorrhagic septicaemia, liquefactive necrosis, skin hyperpigmentation, erythematous lesions, furuncles or ulcers, and organomegaly, particularly of the spleen and liver the furuncle-like lesions, which are primarily seen in chronic infection, have tissue fluid, necrotic tissue and macrophages, which is a fact that differentiates them from the actual furuncles in its homeotherms. In the severe cases, tissue necrosis can occur because of the degeneration of muscles, fragmentation of the fibres and haemorrhage (Izadi and Vajargah, 2022) [19].

This bacterium is very dangerous because it creates exotoxins that can injure fish all over their bodies. The infection usually starts with a lot of bacteria and can end up hurting internal organs badly. Some common indicators that fish are unwell are swimming in weird ways, not eating as much, losing scales, swelling of internal organs, and the formation of bleeding sores (Nikiforov-Nikishin *et al*., 2025) [32].

There are many things like environment, the host's age, and the host's innate immunity all affect how quickly and how badly a disease spread. Fingerlings are especially vulnerable. Keeping the water clean, giving the nutritious food to fish, and making sure they don't become over stressed that will also boost their immune system and lower their risk of infection (Cipriano and Bullock, 2001) [8].

Chloramphenicol, florfenicol, and oxolinic acid are antibiotics that perform well against infections caused by *Aeromonas salmonicida*.

The primary instruments to address this problem are vaccines and antibiotics, yet the excessive usage of antibiotics may alter the balance in the ecological situation and lead to resistance, which is dangerous to the health of aquatic animals (Tan, Chen, and Hu, 2019) [41].

Furunculosis is regarded as a widespread and persistent issue within aquaculture, necessitating ongoing monitoring and the implementation of effective preventative strategies

Vibrio anguillarum

Vibriosis, triggered by *Vibrio anguillarum*, stands out as one of the most devastating bacterial diseases in fish. Common signs include skin darkening and the formation of ulcers. In chronic cases, intense haemorrhages are observed on visceral organs and body muscles. In the body, the spleen may be distended and the kidney made liquid (Manchanayake *et al*., 2023) [29].

The typical external clinical manifestations of vibriosis are loss of body condition, depression, the reddening of the ventral and lateral sides of the animal and swollen dark ulcerated and haemorrhagic lesions. The eyes are also affected, resulting in opacity at first, and later ulceration and exophthalmia. Internally, the intestines may be distended and filled with a clear, viscous liquid, and the pathogen is found in high concentrations in the blood and hematopoietic tissues (Austin & Austin, 2007) [2].

The favourable conditions created due to the high-density cultivation of aquaculture and the pervasive use of antibiotics precondition the appearance of antimicrobial-resistant bacteria (Watts *et al*., 2017) [48]. Practices that involve environmental management, such as proper management of organic waste and proper maintenance of water quality, are significant in curbing the multiplication of pathogenic organisms.

Probiotics can be used as substitutes for antibiotics because they can compete with pathogens and occupy their space and resources, enhance intestinal health in fish, and activate the immune system of fish (Irshath *et al*., 2023) [20].

One of the most widely used therapies of vibriosis currently in aquaculture is the use of antibiotics. But the problem with uncontrolled antibiotic usage is that multidrug-resistant (MDR) bacteria are becoming widespread, which constrains the treatment of bacterial diseases in both animals and humans (Manyi-Loh *et al*., 2018) [30].

Various vaccines against vibriosis have been found to be developed in microbial compounds like probiotics, such as inactivated, live attenuated, and DNA-based vaccines (Abdellatief and Alkalamawey, 2024) [3]. Among them, vaccines against bacterial pathogens which have been inactivated have been the most prevalent in the aquaculture industry because they are very effective against fish.

Conclusion

Aquaculture has come out as the fastest-growing food production industry in the world, and it has become a decisive factor in food security and economic stability of the globe. Salmon and trout are valuable fish species that are needed to contribute to this growth because of their nutritional content and high market value. The rapid development of aquaculture has, however, increased the number of bacterial diseases, especially in low-temperature cold systems, whereby high stocking densities and low temperatures favour the growth of the disease.

The most important threats are gram-negative bacteria that can inflict serious infections culminating in mortality loss and severe economic damages, including *Flavobacterium psychrophilum, Aeromonas salmonicida, Yersinia ruckeri,* and *Vibrio anguillarum*. They weaken the health of fish by causing systemic infections and tissue necrosis as well as a suppressed their immune system, which is mostly caused by environmental stressors like poor water quality and overstocking.

Although there is some degree of control using antibiotics and vaccines against the bacterial infections, their coverage is low at premature stages of life, and resistance by the bacteria. Enhancing biosecurity protocols through better water quality management, optimization of stocking ratio, and generation of sustainable alternatives such as probiotics and next-generation vaccines is necessary to the long-term health, productivity, and sustainability of cold-water aquaculture systems.

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