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Sex is a Crucial Factor in the Immune Response: An Ichthyological Perspective

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ABSTRACT

Sex plays a crucial role in shaping the immune response of vertebrates, leading to differing susceptibilities to diseases between females and males. This review explores the observed sexually dimorphic patterns in different pathogenic infections, immune responses, and molecular events. First, a compilation of historical guidelines for incorporating gender/sex as a variable in research studies to enhance scientific rigor, improve research outcomes, and promote better health for both sexes has been carried out. Following this, the study focuses on examining sex-based differences in immune responses across different taxa, with an in-depth review of available studies on fish, particularly regarding the prevalence of sex-related differences in parasites, viruses, and bacteria. Furthermore, the benefits of considering sexual dimorphism when evaluating the prevalence of diseases in fish management in aquaculture and ecological contexts have been discussed. Integrating sex in understanding immune responses will positively influence fish welfare, economic impacts, and policymaking, leading to more tailored and effective treatments.

KEYWORDS

Dimorphism; epigenetic; fish; infection; prevalence; regulations; sexual

Introduction

Sexual dimorphism is a common phenomenon in animals with separate sexes caused by both ecological and sexual selective factors (Slatkin 1984), defined as a complex of differences in body size, shape, traits, color, and disease expression between individuals of the same species (Mori et al. 2017). Distinct pathogen responses have been mainly attributed to sex differences of the host, such as behavior, immune response, hormones, diet, and resource allocation, but also to parasite selection and adaptations to the host sex (Duneau and Ebert 2012).

Although infectious diseases are widespread throughout the animal world, infection patterns vary among populations and individuals within a population. Heterogeneity in trends of infection is driven by many factors that can be classified mainly into differences in exposure and susceptibility, where the former represents differences in contact probability with pathogens through behavioral or ecological differences, and the latter typically means post-exposure sensitivity differences (Kelly et al. 2018). Individual

characteristics that may determine both exposure and susceptibility are, for example, the physiological condition (Beldomenico and Begon 2010), the age (Krakowka and Koestner 1976), or the sex. Several sex-linked features have been identified for fish, raising questions about adaptations in how to tackle infectious processes through treatments and prevention methods. While sex appears to play a crucial role in susceptibility to pathogens, it was only three decades ago that regulations began considering it for investigation, and it is only within the last ~15 years, that political actions have been enforced to mandate including both sexes in clinical studies. Current guidelines contrast with the historical fact that most of the animal models for human syndromes were primarily studied in males (or using male animal models), and even the sex of the organism of origin of the cell lines has rarely been revealed (Danska 2014).

In fish, the immune dimorphism between sexes has not received all the attention it deserves, and its implications have not been widely considered. There is an urgent need to consider sexual dimorphism

when analyzing immune responses in fish since reproductive and immune systems are interconnected playing sexual-dependent molecular functions (Caballero-Huertas et al. 2021; Chuphal et al. 2023). The immune response of fish can be influenced by a variety of parameters, among which temperature, stress management, fish density, light, water quality, salinity, food, immunostimulants, anthropogenic pollutants, or abiotic parameters associated with climate change are included (Chaves-Pozo et al. 2018; Danion et al. 2018; Le Du-Carrée et al. 2021; Cohen-Rengifo et al. 2022). In addition, infections are modulated by the intrinsic physiological condition at the individual level. Amid this intricate mosaic of factors, the study of the involvement of sex in the exposure and susceptibility to certain infections should be a priority in fish to tackle disease outbreaks.

This review delves into the linkage between the phenomenon of sexual dimorphism and infections by analyzing the differences in exposure, susceptibility, immune responses, and the associated molecular events. By compiling historical guidelines, the importance of incorporating sex as a variable in research is highlighted to improve scientific accuracy and optimize research results. The focus of this manuscript lies in exploring immune differences across taxa, with a particular emphasis on reviewing the available fish studies that highlight sex prevalence concerning different pathogens. Acknowledging the role of sex in fish diseases can help drive advancements in fish management for aquaculture and ecology, leading to enhanced welfare, economics, policymaking, and more effective treatment approaches.

History of sex as a crucial variable in research

On a time scale, considering 'sex' as a fundamental factor for research and medical sciences, and their impacts on society and animal health is a contemporaneous event (Figure 1). Furthermore, the sex of individuals in research for applications outside the medical field applied to humans has been widely underestimated.

For many years, sex was considered a non-trivial biological variable of the patients regarding the treatments they received. Historically, for multiple reasons, women of childbearing age were excluded from clinical trials, and thus, medical research was centered on male physiology (Mauvais-Jarvis et al. 2020). Ignoring aspects of sex in data collection and analysis in clinical trials has had detrimental consequences. One of the most well-known examples is cardiac arrest, wherein men and women encounter distinct sets of symptoms. Unfortunately, the emphasis on men symptoms as the 'textbook' diagnostic criteria has resulted in delayed treatment, diagnosis, and even prognosis analysis for women with fateful consequences (Shansky and Murphy 2021). From the pharmacological perspective, eight out of ten drugs were withdrawn from the United States of America (USA) market in the late 1990s because they had significantly more side effects in women than men (Danska 2014; Bischof et al. 2020). Remarkably, and in contrast to this occurrence, just in the previous years (1993), the National Institutes of Health (NIH) of the USA by Revitalization Act program had required that

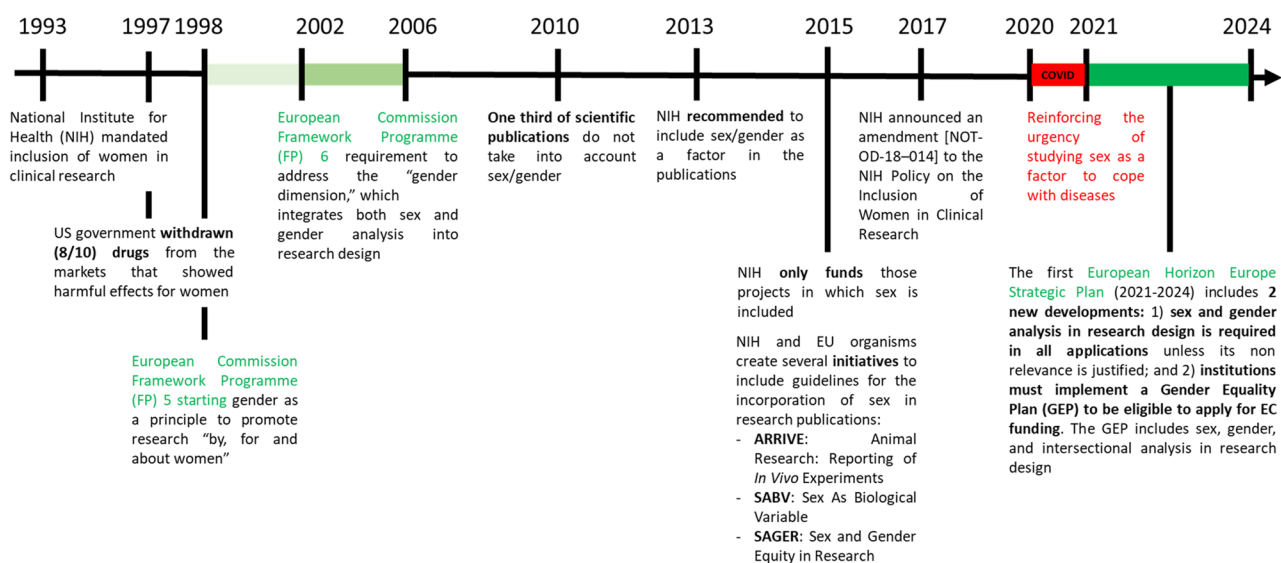


Figure 1. Historical outline of the milestones in the inclusion of sex and gender in biomedical research in the North American and European legislative framework.

NIH-funded clinical trials included women as participants (Geller et al. 2011).

In the European Union (EU), gender mainstreaming principle (“understood in terms of three dimensions: to promote research by, for and about women”) was integrated for the first time into the Fifth European Commission Framework Programme (FP5)—running from 1998 to 2002—, but it was not until the Sixth European Commission Framework Programme (FP6)—running from 2002 to 2006—, that gender mainstreaming was formally integrated into the EU research policy (Rosa et al. 2020). This step definitely initiated a process to include the sex of the model animals for research purposes. Nevertheless, even today, European legislation needs improvement, particularly regarding non-mammal species like fish.

Given the deficiencies in the reflection of sex in scientific projects and publications in many fields, as occurred, for example, in Canada in 2010—where ~80% of applications to Canadian Institutes of Health Research revealed that biological sex was not considered in basic biomedical proposals, governments started to implement these recommendations (Danska 2014). In 2013, NIH initially recommended the inclusion of sex as a factor in publications. Just two years later, NIH adopted a stricter stance, only providing funding for projects that incorporated sex as a significant consideration.

Consequently, NIH and EU organisms created several initiatives for the development and application of guidelines to include sex in scientific publications. This is the case of ARRIVE (Animal Research: Reporting of *In Vivo* Experiments) guidelines funded by the National Center for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs) in the United Kingdom. The ARRIVE guidelines were developed to improve the quality of reporting in scientific publications that involve research using animals. These guidelines consist of a checklist of 20 items designed to ensure the minimum information necessary to be present in publications. Examples of these items include sex, gender, strain, and genetic background, housing and husbandry, experimental procedure, statistical and analytical methods. Moreover, NIH-funded Research created the Consideration of Sex as a Biological Variable (SABV) policy, which states that sex and gender are biological variables required in research designs, analyses, and reports in vertebrate animal and human studies (Clayton and Collins 2014; Clayton 2018). In this line, the European Association of Science Editors (EASE) published in 2016 the SAGER guideline to provide a comprehensive procedure for reporting sex and gender

information in study design, data analysis, results, and interpretation of findings (Becher and Oertelt-Prigione 2022).

In parallel, in the USA the Food and Drug Administration (FDA, <https://www.fda.gov/>), which regulates all prescription drugs and devices, issued an Action Plan incorporating to some degree the study of sex differences in the approval process for drugs and devices. In 2017, a significant step was taken to improve the representation of women in research studies and improve male-skewed bias. The NIH implemented new guidelines and requirements to address the historical underrepresentation of women in clinical trials and research using animal models and cell studies. These requirements aimed to ensure that women were adequately represented and considered in biomedical research, acknowledging the potential sex-based differences that can influence health outcomes and treatment responses.

In contrast to all the efforts made since the last world health crisis with SARS-CoV-2 (COVID-19) and the rush to advance solutions, treatments and prevention for this viral infection revealed the lack of policies regarding the inclusion of sex in biomedical research. Shocking data exists in this regard, as a publication by Brady et al. (2021) registered 4,420 COVID-19 studies of which 935 (21.2%) addressed sex/gender solely in the context of recruitment, 237 (5.4%) planned sex-matched or representative samples or emphasized sex/gender reporting, 178 (4%) only explicitly reported a plan to include sex/gender as an analytical variable, and the resting publications sex was not even mentioned. The poor incorporation of sex and gender into COVID-19 research was also shared by Heidari et al. (2021), who analyzed 75 clinical trials on COVID-19 vaccines. Only 24% presented their main outcome data disaggregated by sex, and only 13% included any discussion of the implications of their study for women and men. These data are paradoxical since infection fatality rate and risk of death from COVID-19 varied in men (3.17%; 1,274,663) vs. women (2.26%; 971,899) in 73 countries during 2020–2021 (Ramírez-Soto et al. 2021), thus a higher prevalence of infection was observed in men (Mukherjee and Pahan 2021). Undoubtedly, the most severe pandemic of this century has highlighted the inadequacy of overlooking sex as a crucial factor in research, underscoring the pressing need to investigate sex as a significant variable in addressing human diseases. Further examples of the relevance of sex in the variations in immunological, hormonal, genetic, and microbiota profiles between males and females could impact vaccination efficacy. This is the case of the

vaccines against Human Immunodeficiency Virus (HIV-a) in humans (Klein et al. 2015; Ziegler and Altfeld 2016), for which the role of sex and sexual hormones in regulating the innate immune responses is evident.

Currently, one of the most impactful innovations in the EU Framework program Horizon Europe is the introduction of a Gender Equality Plan (GEP) starting February 2022. Under this framework, applicants requesting funding under Horizon Europe are required to have a GEP in their organization (Becher and Oertelt-Prigione 2022). In this context, many research institutes are engaged in promoting gender policies inside their establishment. This one should contain the description of the integration of four mandatory process-related requirements: a public formal document, dedicated resources, data collection and monitoring, and training. Among the non-mandatory/recommended requisites is the integration of the gender dimension into research and teaching content. This includes “the commitment to incorporating sex and gender in its research priorities, the processes for ensuring that the gender dimension is considered in research and teaching, and the support and capacity provided for researchers to develop methodologies that incorporate sex and gender analysis” (European Commission 2020). Regrettably, still nowadays in the middle of the twenty first century, many efforts need to be made to integrate sex equality in research.

Immune dimorphism: an overview across taxa

It is documented that the innate and adaptive immune responses developed against infections or in the context of autoimmune diseases commonly differ between females and males (Klein and Flanagan 2016). A large amount of information supports the fact that hormones of the endocrine system are involved in the immunological dimorphism between males and females. Sex differences in immunity may also depend upon the considered taxa, particularly because of the existence of very different immunological mechanisms among species (Jaillon et al. 2019). These variances can also be observed in closely related species or among populations due to life-history differences (Kelly et al. 2018). The extent to which the relationship among hormones, secondary sex traits, and the immune system exists may be related ultimately to the mating system, the degree of sexual conflict, and potentially, to the fertilization mode (Klein 2000; Barribeau and Otti 2020). The classic example provided by Bateman (1948) illustrates that females *Drosophila* maximize fitness by longevity by investing in their immunity, whereas males maximize fitness by increasing the mating rate, to the detriment of their defense capabilities (Rolff et al. 2005).

Sexual dimorphism is present in infections and the immune response throughout evolution, both in invertebrates and vertebrates (Nunn et al. 2008) (Figure 2). In crustacean *Nephrops norvegicus*,

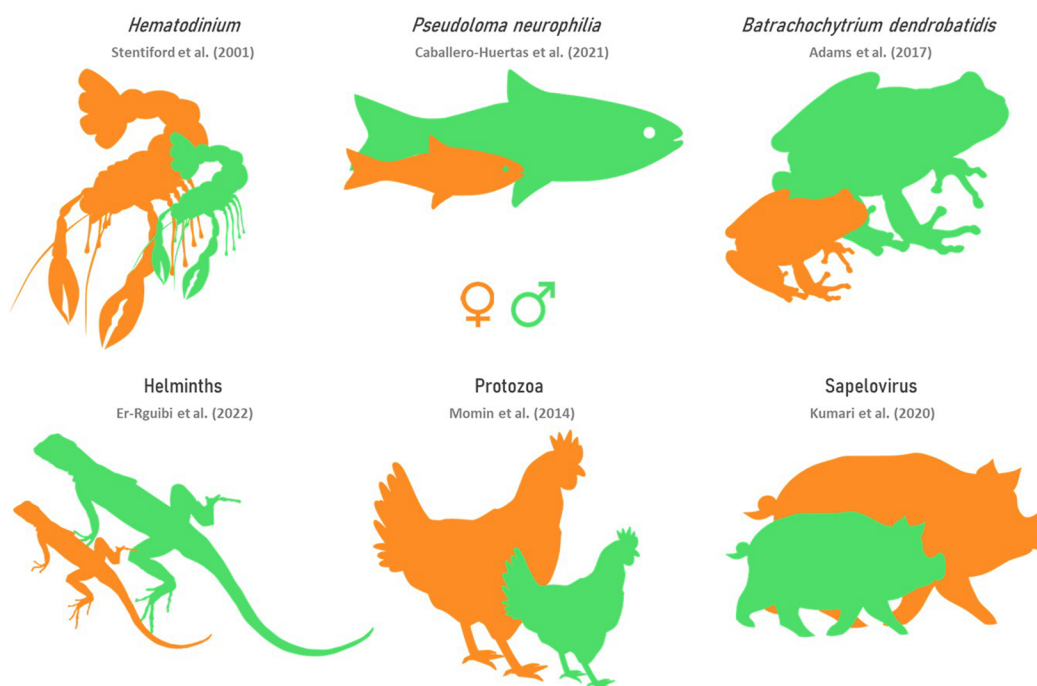


Figure 2. Examples of the sexual dimorphism in pathogen prevalence across taxa.

infection prevalence of a dinoflagellate parasite was synchronous between the sexes in some months but more females were infected in spring (Stentiford et al. 2001), which corresponds to the pre-laying period (Farmer 1974). In amphibians, studies have shown that males and females can display differences in immune system function and response. In natterjack toads (*Epidalea calamita*) artificially challenged with an innocuous antigen, swelling response magnitude, used as a proxy of inflammatory response short-term progression, did not differ between males and females, although female swelling response peaked earlier (Zamora-Camacho 2019). In *Rana catesbeiana*, adult males were more likely to be infected by the chytrid fungus *Batrachochytrium dendrobatidis* than either females or juveniles (Adams et al. 2017), but whether the sexual dimorphism could be related to the decline of the amphibian populations needs further research. In lizard (*Chalcides mionecton*), infections by helminths are more prevalent in males because of a phenomenon of sniffing of fecal pellets of other lizards by males and a tongue-contact facilitating transmission and ingestion of helminth eggs into the digestive tract, a behavior not present in females (Er-Rguibi et al. 2022). Moreover, in another reptile, the hissing sand snake (*Psammodphis sibilans*), it has been observed the highest lymphocyte response in females in almost all comparative tests (primary anti-rat erythrocytes antibody response, ConA, PHA, and LPS) that evaluate immune reaction (Saad and Shoukrey 1988).

An enhanced immune reactivity in females is typical for mammals and birds (Moore and Wilson 2002; Vincze et al. 2022), which help mount an effective resistance to infection. As a result, females are generally less susceptible to infections but can develop immune-pathogenic effects and a predisposition to autoimmunity due to hyperimmune responses (Morrow and Innocenti 2012; Taneja 2018). In this context, studies of haemoprotozoan infection in domestic pigeons recorded higher prevalence in males than female birds (Dey et al. 2010; Hasan et al. 2017). Nevertheless, higher protozoa infection rates in females than males were recorded in this species in other studies (58.22% females vs. 48.79% males) (Saikia et al. 2019), as well as similar results in poultry infections (46.5% females vs. 44.8% males, Figure 2) (Momin et al. 2014). Furthermore, viral infection by sapelovirus in pigs revealed higher sex prevalence in females (25%) when compared to males (22.85%) (Kumari et al. 2020). Thus, despite general patterns in the performance of the immune system within a specific taxon and broadly within a specific sex, it is

crucial to recognize the unique aspects tied to pathogens, species, infection processes, and host characteristics that required further investigation. These particularities significantly influence the dynamics of immune responses, highlighting the need for in-depth studies to comprehend the complexities of host-pathogen interactions.

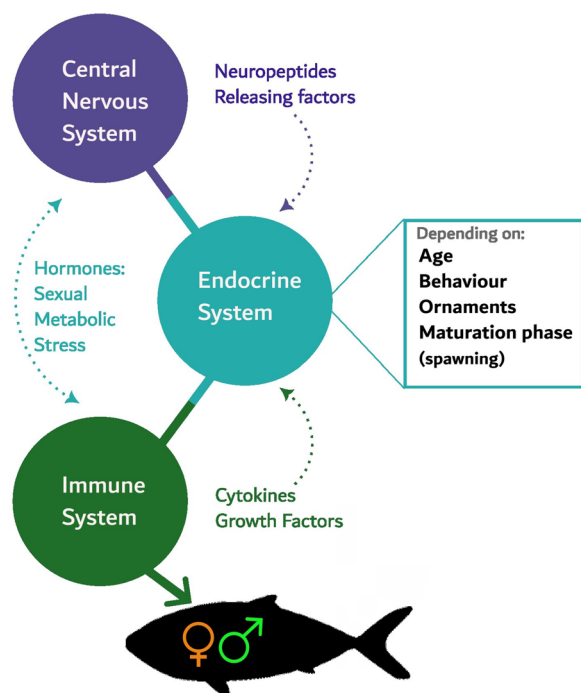
Linking fish traits to sexual immune dimorphism

Teleost fish/fishes display the most striking reproductive variety of all vertebrates (Smith and Wootton 2016) with a wide diversity of reproductive strategies, fertilization modes, and breeding behaviors. Most of the fish species are gonochoristic, an individual is a male or a female, and sex can be determined genetically, but also the environment may have an influence on the gonadal development (Stelkens and Wedekind 2010; Penman and Piferrer 2008). Hermaphroditism represents 370 families of fish species, predominantly among tropical and marine perciforms and few numbers of fish species are unisexual (De Mitcheson and Liu 2008; Pla et al. 2021). External fertilization is the most common, although, in about 500–600 species, it takes place internally, as in Chondrichthyes (Wootton and Smith 2014). In addition, the context of the selection of partners by the mating fish varies across species, and also it is particularly associated with parental care after the fertilization of eggs (Smith and Wootton 2016). The diversification in teleost in nearly 30,000 fish species is one of the main reasons that spark interest in the study of sex-linked immunity in these species. Within the same infraclass, a great variability is to be expected in the way in which the immune system is conditioned by sex based on other factors of the life history of the species and the characteristics of their reproductive physiology and behavior.

This section is focused on how fish sexual differences may affect the exposure and susceptibility to the development of infections. Differential exposure related to the sex of the host can occur due to certain dimorphic characteristics in males and females, such as behavior, development of ornaments or structures related to sexual selection, specificity of organs (testicles or ovaries), the availability of individuals of either sex in the system, as well as the size of each sex and their lifespan. In this context, differences in immunity in males and females are the result of these characteristics alone but also their interactions (Table 1). Remarkably, interactions among the central nervous system, endocrine, and immune systems are

Table 1. Features linked to sex that potentially affect the exposure and susceptibility of an infection in cultured fish.

Host sex-linked features		Examples
Exposure	Behavior	The aggressiveness of males is related to high cortisol levels, compromising their immune system and favoring the infectious capacity of the colonizing organism. e.g., zebrafish with <i>Pseudoloma neurophilia</i> (Chow et al. 2016)
	Ornaments	Linked to testosterone, the expression of ornaments increases fitness, but at the same time, it suppresses immune function. e.g., three-spined stickleback (Kurtz et al. 2007)
	Organ specificity	Certain parasites are specific to organs present in either sex. e.g., testes infection by <i>Sphaerospora testicularis</i> in gilthead seabream (Sitja-bobadilla and Alvarez-pellitero 1990; Castro et al. 2018)
	Lifespan	Females have longer telomere length and lifespan than males, there are more possibilities to suffer from infection. e.g., medaka (Gopalakrishnan et al. 2013)
	Host body size	Parasite intensity usually increases with fish size. e.g., cestodes, digenean, acanthocephalans, and nematodes in Nile tilapia (<i>Oreochromis niloticus</i>) and African catfish (<i>Clarias gariepinus</i>) (Akoll et al. 2012), and size may be linked to sex, as in Nile tilapia (bigger males) (Toguyeni et al. 1997)
	Host availability	In cultures that only work with one sex, the parasites will only have access to it. e.g., Monosex stocks, as all-male production in Nile tilapia, catfish, or guppies (Cnaani and Levavi-Sivan 2009)
Susceptibility	Immunocompetence	Sexually mature male salmon are significantly more frequently or severely infected with ectoparasites than mature females are, which is linked to androgen-induced loss of goblet cells, exacerbating parasitic infestations (Pickering 1989)
	Reproductive maturation	The gonadal cycle can trigger changes in fish immune responses associated, among others, to sex hormones and cortisol. e.g., interrenal tissues from a spawning female and a sexually mature male presented marked sexually dimorphic cortisol responses <i>in vitro</i> , in which female chinook salmon and rainbow trout had greater responses to stimulation (McQuillan et al. 2003)
	Genetic manipulation	Triploid individuals may affect the immune capacity to deal with infections (e.g., triploid coho salmon showed a lower resistance to vibriosis than their diploid counterparts, Jhingan et al. 2003)

**Figure 3.** Outline of the interactions between the central nervous system, endocrine, and immune systems of fish. Adapted from Campbell et al. (2021).

important for a wide variety of processes affecting the development of the characteristic traits of both sexes (e.g., age and behavior) (Figure 3). Neuropeptides and releasing factors (e.g., corticotrophin-releasing factor, adrenocorticotrophic hormone, α -melanocyte stimulating hormone, and β -endorphin) can interfere with the central and endocrine system, ultimately modulating fish immune response (Berczi et al. 1996). Recurrently, sexual hormones (e.g., estrogen,

testosterone, gonadotropin release hormone, GnRH), stress hormones (e.g., corticosteroids and ACTH), metabolic hormones (e.g., insulin growth factor, IGF), and pituitary hormones (e.g., growth hormone, GH, prolactin) occupy a central role in the different sexual features modulating immune activity (Tokarz et al. 2015; Campbell et al. 2021). Furthermore, cells within the neuronal and endocrine systems can express receptors to immune-derived cytokines (e.g., TNF), chemokines, and growth factors (Taub 2008). Thus, the communication and regulation between the reproductive and the immune systems is multidirectional.

Social hierarchies are widespread, including in many fish species, which enhance access to limited resources, including food and mates, and can therefore be an important determinant of individual fitness (Filby et al. 2012). In fish, behavior is closely linked to this hierarchical structure and is characteristic of each taxon although it can be altered in a culturing system in which different behavioral phenotypes and the selection for inherited behavioral traits over several generations could be found (Huntingford 2004). It is known that fish personality matter in the response of the immune system as proactive (adrenaline-based response) fish (*Oncorhynchus mykiss*) in comparison to reactive (cortisol-based response) fish mate in the tank, showing higher expression levels of genes related to the innate immune system (MacKenzie et al. 2009). In this line, agonistic behavior—social behavior related to fighting—can either increase (e.g., brook trout, *Salvelinus fontinalis*; coho salmon, *O. kisutch*; or cut-throat trout, *O. clarki*) or decrease (e.g., medaka,

Oryzias latipes; or Atlantic salmon parr, *Salmo salar*) with domestication (Ruzzante 1994).

In some species, agonistic behavior is linked to males and tightly related to the reproductive capacity (Desjardins et al. 2012), even though the size might contribute to the formation of dominance hierarchies and not sex itself (Spagnoli et al. 2015). Nevertheless, the hormonal profile, highlighting 11-ketotestosterone as the main androgen in male fish and the most associated with aggression and dominance, is determinant (Filby et al. 2012). This hormone is related to several features of male phenotype including the development of ornaments to favor selection by females. Despite its advantages in reproduction, the production of male-related hormones is associated with a high degree of stress as a result of the triggering of cortisol. Stress responses are associated with substantial energetic costs, particularly under conditions of repeated and chronic stress, leading to impaired disease resistance and delayed immune response (Segner et al. 2012; Niklasson 2013). In this sense, the expression of ornaments in three-spined stickleback (*Gasterosteus aculeatus*) increases fitness but at the same time, it suppresses immune function, which was defined by Kurtz et al. (2007) as the immunocompetence handicap hypothesis. In addition, a study of zebrafish showed that elevated cortisol increased the susceptibility of males in comparison to females to be infected of a microsporidian parasite (Chow et al. 2016).

On the other hand, certain pathogens are specific to tissues and organs present in either sex as, for example, the infection by *Sphaerospora testicularis* in European sea bass, *Dicentrarchus labrax* (Sitja-bobadilla and Alvarez-pellitero 1990; Castro et al. 2018), which is exclusive of testicular tissue and can be responsible for the parasitic castration of the host. On the contrary, bacterial *Vibrio gigantis* growth was observed in the ovary samples of the female European seabass, while it was not present in the gonad samples of males, but it was also isolated from the liver and spleen of both sexes (Yilmaz et al. 2023). In this sense, it will be the nature of the pathogen that determines not only the effects on the host physiology, but also its potential to be transmitted vertically by females, males, or both (e.g., Valero et al. 2018; Caballero-Huertas et al. 2021).

Although the more sensitive stages for a lot of pathogens (particularly viruses) are larvae and juveniles (Vadstein et al. 2013), lifespan is another factor to be considered. It is usually longer in females (and generally associated with sex and sexual hormones), therefore increasing the possibility of pathogen encounters (e.g., medaka) (Gopalakrishnan et al.

2013). Likewise, it has been shown that with aging, changes occur in the microbiota, which is of great importance for disease resistance and immune function. Piazzon et al. (2019) showed differences in adult gilthead sea bream intestinal microbiota composition among age categories. Moreover, this modulation in intestinal species was also related to the sequential sex change from male to female.

In addition, parasite intensity usually increases with fish body size, and size may be related to sex, as in Nile tilapia (*Oreochromis niloticus*), in which bigger males are found (Toguyeni et al. 1997). Thus, bigger individuals presented more pathogens such as cestodes, digeneans, acanthocephalans, and nematodes in tilapia and African catfish, *Clarias gariepinus*, (Akoll et al. 2012). In this line, the infection can go beyond the symptoms, affecting the general vulnerability of individuals, which is connected in turn with the size and body condition. An interesting study by Stephenson et al. (2016) showed that size differences should be accounted for when examining dimorphism. In this work, the escape response of fish was measured after infection with the ectoparasite *Gyrodactylus turnbulli*. The result implied that parasite-induced vulnerability to factors such as predation in male-biased (larger phenotype), but when size was controlled, there was no difference in the escape response among sexes. Another aspect to explore in the body size is the impact of hermaphroditism in the sexual prevalence as the sex change requires multifactorial events. Specifically, studying how prevalence varies with the sex change and its relation with the body size and the immune response remains deeply to be explored.

The availability of unique host sex, that is, the consequence of the interest to obtain monosex populations to increase fish productivity (e.g., all-male production: Nile tilapia, catfish, guppies; all-female: trout, salmon, common carp, Cnaani and Levavi-Sivan 2009), causes pathogens to infect only one sex. In monosex male cultures, androgens had the potential effect of decreasing immunity, so special attention should be paid to cultures in which the main interest lies in one sex because of faster growth, for example, in tilapia (Toguyeni et al. 1997). These culture systems might contain a reduced proportion of immunocompetent individuals compared to mixed productions (males and females), potentially leading to an increase in the probability of pathogens proliferation. In this regard, in addition to being used for the induction of reproduction, the exogenous sex steroid hormones used in aquaculture practices to induce monosex, as in tilapias, Pacific salmonids (genus *Oncorhynchus*), flatfishes, or sea basses (Luckenbach et al. 2017), have

been shown to impact the development of immune organs in several fish species when exposed at early stages (Seemann et al. 2013; Campbell et al. 2021). Focusing on the use of androgens for this purpose, methyltestosterone (MT) is an endocrine disruptor broadly used in sex-reversal when there is an interest in producing male individuals, commonly used in Nile tilapia (El-Greisy and El-Gamal 2012), and also to produce all-female populations including masculinized female (XX males) in salmonids (Feist et al. 1995). Nile tilapia mono sex cultures have been reported a low level of red blood cells and lymphocytes, to which is added the disruptive effect of MT in antioxidant enzyme activities and gene transcription following exposure or dietary intake in fry (Abo-Al-Ela 2018). Moreover, the administration of testosterone or dihydrotestosterone post-castration led to the inhibition of thymic rejuvenation as well as a reduced proliferation of thymic T-cells coupled with increased apoptosis, with plasmatic hormone levels negatively correlated with the leukocyte response (Abo-Al-Ela et al. 2017). Moreover, gene networks related to innate immune responses are affected by dihydrotestosterone treatment, as seen in the fathead minnow (Ornostay et al. 2016).

In addition, susceptibility, which refers to the sensitivity of a host after exposure to an infectious agent, can be modulated by the sexual dimorphism of the immunocompetence (Table 1). The historical explanation for males exhibiting lower immunocompetence has often attributed it to proximate physiological factors, notably the suppressive effects of the male hormone testosterone (Stoehr and Kokko 2006), which increases susceptibility to infections and their morbidity. In addition to the effect of reproductive hormones and their interactions with cortisol, other circulating hormones such as growth hormone, prolactin, melanin-concentrating hormone, and proopiomelanocortin-derived peptides have all been shown to influence immune functions in several fish species (Harris and Bird 2000). For example, the higher prevalence of ectoparasites in sexually mature male salmonids compared to mature females was partly linked to androgen-induced loss of goblet cells, which exacerbates parasitic infestations (Pickering 1989). Moreover, it was observed that testosterone was able to modify the production of cytokines, decrease toll-like receptor (TLR) 4 expression in macrophages (MØ), alter the sensitivity of these cells to TLR4 ligands, and involve the phagocytosis in gilthead seabream (Aguila et al. 2013). The presence of immune cells and cytokines in the gonads of this species supports and modulates the reproductive functions by

stimulating their extravasations from the blood, in which testosterone but also 17-beta estradiol seem to be involved (Chaves-Pozo et al. 2005, 2008). Moreover, leukocytes incubated from the head kidney of juvenile spring chinook salmon (*Oncorhynchus tshawytscha*) together with testosterone impacted fish immunocompetence by decreasing the ability to form specific antibody-producing cells (Slater and Schreck 1993).

Furthermore, reproductive maturation is known to trigger changes in fish immune responses associated, among others, with changes in sex hormones and cortisol levels, which could involve differences according to sex (Campbell et al. 2021). When considering the interactions between fish reproduction and parasites with a complex life cycle, it could be observed seasonal patterns of infection compatible with host reproduction associated immunosuppression that could suggest evolutionary host-parasite interactions (Simkova et al. 2005; Caballero-Huertas et al. 2023). Semelparous chinook salmon increases cortisol release during sexual maturation, which may be related to the rapid senescence that occurs after spawning because elevated cortisol is accompanied by energy depletion and reduction of the immune capacity, increasing their susceptibility to parasites and pathogens (Couch et al. 2022). In this context, interrenal tissue, one of the principal immune organs in fish, presented marked sexually dimorphic cortisol responses *in vitro*, in which mature female chinook salmon and rainbow trout had a greater response to stimulation when compared to mature males (McQuillan et al. 2003). Additionally, several immune molecules (inflammatory molecules, anti-inflammatory cytokines, innate immune receptors, lymphocyte receptors, an anti-viral molecule, and molecules related to leukocyte infiltration) detected in the testicular tissue of gilthead seabream, a protandrous species, showed a pattern of expression that depends on the reproductive stage of the first two reproductive cycles when the fish develops and functions as male (Chaves-Pozo et al. 2008). More susceptibility to infections in females than males was observed in stone loach (*Barbatula barbatula*) in periods of higher reproductive investment, probably associated with higher energy devoted to gonad maturation (Simkova et al. 2005) to the detriment of the organism defense. Leucocytopenia, decreased number of plasmacyte cells, and low plasma Immunoglobulin M levels were observed during the spawning season in rainbow trout, and were correlated with elevations in plasma cortisol, testosterone, and estradiol-17β in females and cortisol, testosterone, and 11-ketotestosterone in males (Hou et al. 1999).

Last but not least, it is relevant to consider genetic manipulation to improve aquaculture production as it can generate different fish susceptibilities. This is the case of triploidism in male plaice, *Pleuronectes platessa*, in which the immune capacity to deal with infection was affected, or the triploid coho salmon, which showed a lower resistance to vibriosis than their diploid counterparts (Jhingan et al. 2003). Nevertheless, it is worth describing that for triploid animals, sex would not be the determinant factor, but its chromosomal condition.

Prevalence of fish pathogens in the sexes

Fish infection prevalence by sex refers to the differing rates and outcomes of infections between males and females. It involves deciphering the variations in susceptibility, severity, and occurrence of infections based on sex. Understanding the sex prevalence in fish infections is of high importance for fisheries management, aquaculture practices, and conservation efforts. This is why the development and application of regulations are fundamental.

As previously described in this review, it is important to note that the prevalence of pathogens in fish can be influenced by numerous factors beyond sex, including, among others, immune status, environmental conditions, host genetics, and pathogen transmission dynamics. Therefore, a comprehensive understanding of pathogen prevalence requires a multifactorial approach. The existing literature highlights several factors that contribute to the observed sex-based differences in infection prevalence among fish species. Further, the prevalence of specific pathogens can vary greatly depending on the fish taxon, geographic location, environmental conditions, and other factors that also may be interlinked.

It is worth noting that the number of studies examining such sex-specific infection prevalence remains limited. Surprisingly, in most of the available studies, sex prevalence data need to be sought in the publication as it is not described clearly. While many studies addressed the infections in fish, few of them addressed the sex prevalence. In general, the papers detailed factors such as age, size, season, temperatures, and location, but few data regarding sex influence are considered. To shed light on the available information regarding the sex prevalence in fish infections, a search of the available data was carried out to obtain a general perspective based on the types of infections in fish: parasitic, viral, and bacterial. The bibliographic search encompassed both Web of Science and Google

Scholar databases without restriction by years. As a result of this rigorous inquiry (Table 2), it was found that parasitic studies had the highest number of research investigations, totaling 29, four of them with no significant differences (NS, $p > 0.05$) between sexes, followed by viral studies with six papers, being two of them without significant differences (NS, $p > 0.05$) between males and females. Bacterial studies resulted, surprisingly, with only two publications in which sex was considered a factor in the data analysis (Table 2). Figure 4 shows the sex prevalence based on fish species and different pathogenic infections exclusively incorporating statistical significance in the published data ($p < 0.05$). Analyzing prevalence with a focus on sex, it was found that in 53.6% of the publications on parasitic infections females were preferentially targeted, versus 46.4% of males (Figure 4). For viral infections, 75% displayed a significantly higher prevalence in males, leaving only 25% affecting females. The investigated bacterial infections exhibited a 100% preference for females due to the low number of publications found. Thus, the inclusion of additional research in this area will alter the percentages in the future. Additionally, most of the studies reported in the present manuscript analyzed wild fish species, with only six focused on cultured species.

It is worth mentioning that when confirming higher prevalence in one sex over the other, it is essential to complement this information with a survival analysis stratified by sex to mitigate survivorship bias. For example, more pathogens may be found in females because males with potentially weaker immune systems could die at a higher proportion. Vollset et al. (2021) suggested that low pathogen loads in wild fish could be due to survivor bias, as sick individuals are quickly eliminated by predators and remain uncounted. Furthermore, the unequal distribution of pathogens between females and males could mask the actual sex-based prevalence.

Parasitic infections

Duneau and Ebert (2012) described three different paths of parasite adaptation according to host sexual dimorphism: (1) parasites that adapt differently to each sex, leading to dimorphism in the parasite population, or “host sex-specific dimorphism”, (2) parasites that specialize on only one sex, or “single-sex specialization”, and (3) parasites with phenotypically plastic traits, whose expression is dependent on the sex of their host, or “plastic sex-specific disease expression”. Generally, it was observed the first path among publications, in

Table 2. Compendium of studies showing the unequal prevalence of pathogens according to the sexes in different fish species.

Species	Fish origin	Pathogen	Infection	Sex of higher prevalence	Reference
<i>Alburnoides manyasensis</i>	W	P	<i>Paradiplozoon homoion</i>	F	Aydogdu et al. (2020)
<i>Barbatula barbatula</i>	W	P	<i>Gyrodactylus</i> spp., <i>Raphidascaris. acus</i>	F	Šimková et al. (2005)
<i>Capoeta antalyensis</i> , <i>C. caelestis</i> , <i>C. angorae</i>	W	P	<i>Allocreadium isoporum</i>	M	Aydogdu et al. (2018)
<i>Carassius auratus</i> L., <i>Oreochromis niloticus</i>	C	P	Myxozoa, Ciliophora	F	Saha et al. (2015)
<i>Chelon labrosus</i>	W	P	<i>Neoechinorhynchus agilis</i>	M	Aydogdu et al. (2015a)
<i>Clarias gariepinus</i>	W	P	Flagellata, Dinoflagellata, Trematoda, Copepoda, Nematoda, Motile ciliata, Protozoan, Sessile ciliata and Oomycota	F	Amos et al. (2018)
<i>Clarias gariepinus</i> , <i>Tilapia zillii</i>	W	P	Monogenea, Cestode, Nematodes, Acanthocephala	F	Mgbemena et al. (2020)
<i>Clupea harengus membras</i>	W	P	<i>Anisakis simplex</i>	M	Podolska and Horbowy (2003)
<i>Danio rerio</i>	C	P	<i>Pseudoloma neurophilia</i>	M	Spagnoli et al. (2015)
<i>Danio rerio</i>	C	P	<i>Pseudoloma neurophilia</i>	M	Chow et al. (2016)
<i>Dicentrarchus labrax</i>	W	P	<i>Sphaerospora dicentrarchi</i>	F	Castro et al. (2018)
<i>Dicentrarchus labrax</i>	W, C	P	<i>Sphaerospora testicularis</i>	M	Sitja-bobadilla and Alvarez-pellitero (1990)
European marine fish *	W	P	<i>Cryptosporidium</i>	F	Certad et al. (2019)
<i>Gasterosteus aculeatus</i>	W	P	<i>Cyathocephalus truncatus</i> , <i>Bunodera</i> sp.	M	Reimchen and Nosil (2001)
<i>Hydrocynus forskahli</i>	W	P	<i>Schistocephalus solidus</i> , Nematodes	F	Otachi et al. (2015)
<i>Halichoeres bivittatus</i> , <i>Halichoeres garnoti</i> , <i>Halichoeres poeyi</i> , <i>Thalassoma bifasciatum</i>	W	P	<i>Contracaecum</i> sp.	F	Swearer and Robertson (1999)
<i>Mullus barbatus ponticus</i> *	W	P	<i>Kudoa ovivora</i>	F	Swearer and Robertson (1999)
<i>Oreochromis niloticus</i> , <i>Tilapia zillii</i> , <i>Sarotherodon galilaeus</i>	W	P	Metazoan parasite sp.	F	Öztürk and Yesil (2017)
	W	P	Helminths (6 species): <i>Euclinostomum heterostomum</i> , <i>Clinostomum tilapiae</i> , <i>Neascus</i> , <i>Allocreadium ghanensis</i> , <i>Phagicola longa</i> and <i>Alloglossidium corti</i>	F	Simon-Oke (2017)
<i>Oncorhynchus kisutch</i>	W	P	<i>Ceratonova shasta</i>	F	Teffer et al. (2019)
		B	<i>Parvicapsula minibicornis</i> , <i>Ichthyophthirius multifiliis</i> , <i>Kudoa thyrssites</i> , <i>Rickettsia-like organism</i>		
<i>Oncorhynchus nerka</i>	W	V	<i>Infectious Hematopoietic Necrosis Virus</i> (IHN)	F	Grischkowsky and Amend (1976)
<i>Oncorhynchus tshawytscha</i>	W	B	<i>Aeromonas salmonicida</i> , <i>Renibacterium salmoninarum</i>	F	Loch et al. (2012)
<i>Oreochromis niloticus</i> *	W	P	Trematode, Protozoa, Acanthocephala	M	Abd-ELrahman et al. (2023)
<i>Oreochromis niloticus</i> , <i>Tilapia zillii</i> *	W	P	<i>Heterostomum</i>	M	Amaechi (2015)
			<i>Euclinostomum</i> , <i>Clinostomum tilapiae</i>		
<i>Platichthys flesus</i>	W	V	<i>Lymphocystis</i>	M	Vethaak and Jol (1996)
<i>Pseudophoxinus crassus</i>	W	P	<i>Pomphorhynchus laevis</i> , <i>Gyrodactylus laevis</i>	M	Aydogdu et al. (2014)
<i>Rutilus rutilus</i>	W	P	<i>A. immitans</i>	F	Wiklund et al. (1996)
<i>Rutilus rutilus</i>	W	V	<i>Pleistophora mirandellae</i>	F	Wiklund et al. (1996)
<i>Sarotherodon melanotheron</i> , <i>Hemichromis fasciatus</i> , <i>Oreochromis niloticus</i> , <i>Sarotherodon galilaeus</i> , <i>Tilapia zillii</i>	W	P	<i>Papilloma</i>	M	Kortet et al. (2002)
			<i>Clinostomum marginatum</i>	M	Akinsanya et al. (2002)
<i>Salmo gairdneri</i> *	C	V	<i>Infectious Hematopoietic Necrosis Virus</i> (IHN)	F	Amend (1975)
<i>Salmo salar</i> *	C	V	<i>Infectious pancreatic necrosis virus</i> (IPNV)	F	Munro et al. (2010)
<i>Salmo salar</i>	W	V	<i>Piscine reovirus</i>	M	Garseth et al. (2013)
<i>Salmo trutta</i>	W	P	<i>Discocotyle sagittata</i>	M	Paling (1965)
<i>Salmo trutta</i>	W	P	<i>C. farionis</i> (Helminths)	M	Thomas (1964)
<i>Squalius anatolicus</i>	W	P	<i>P. laevis</i>	M	Aydogdu et al. (2015b)
<i>Thalassoma bifasciatum</i>	W	P	<i>Kudoa ovivora</i>	F	Schärer and Vizoso (2003)
<i>Tilapia zillii</i>	W	P	<i>Cucullanus</i> sp.	F	Bamidele et al. (2016)

No significant result between sexes (*); Wild (W); Cultured (C); Parasite (P); Virus (V); Bacteria (B); Male (M); Female (F).

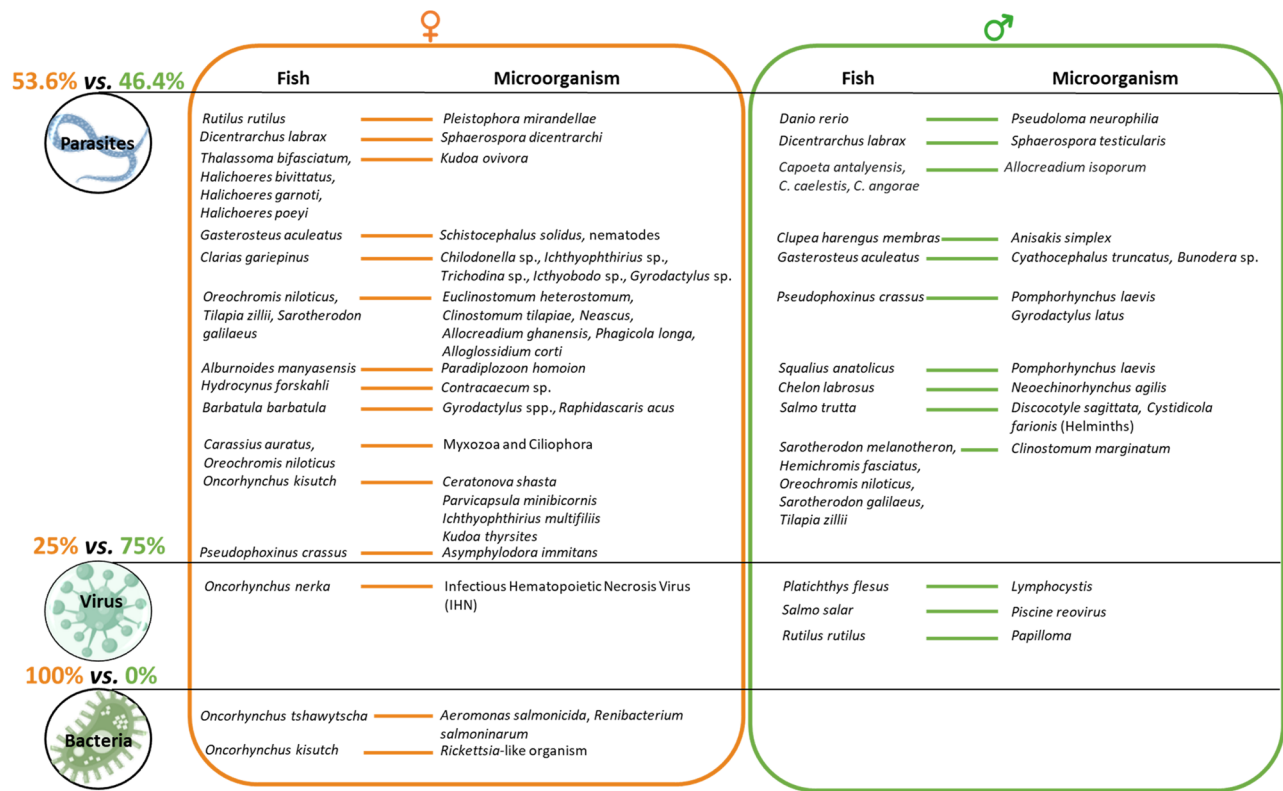


Figure 4. The literature presents examples of sex prevalence in fish species concerning parasites ($n=29$), viruses ($n=6$), and bacterial ($n=2$) infections. The percentage of studies indicating significantly higher infection rates (prevalence) in males or females is highlighted. Please, note that these percentages are based on an exhaustive search of the bibliography, with references for each study provided in Table 2. Nevertheless, it is important to acknowledge that some studies may not have been captured by the search and that incorporating more studies in this field might vary the percentages.

which the evolution of the parasite divergence in a sexual host depends mainly on the extent to which the host is sexually dimorphic and the likelihood of a parasite encountering the opposite sex.

Pseudoloma neurophilia, a prevalent and endogenous parasite affecting the central nervous system, causes many problems in most of the zebrafish facilities around the world (Caballero-Huertas et al. 2021). Detection of *P. neurophilia* usually occurs when irreversible morphological and/or behavioral symptoms appear, leading to the inevitable spread of the infection across rearing tanks. The pathogenic effects of parasitic infections present a sexual dimorphism in favor of males (i.e., a significantly higher proportion (12.4% more than females) of infected males among the total individuals examined (Chow et al. 2016)), and potential transgenerational implications are highlighted due to the vertical transmission of the parasite through the female (Sanders et al. 2013; Spagnoli et al. 2015; Midttun 2020). Nevertheless, *P. neurophilia* similarly reduced fecundity in male and female infected fish (Ramsay et al. 2009; Sanders et al. 2020).

It is crucial to highlight that even within the same host species, parasite prevalence according to sex can

vary depending on the species of the organism that attacks them. A clear illustration of this phenomenon can be observed in the fish species Fat spring minnow (*Pseudophoxinus crassus*). In this case, the prevalence of different kinds of parasites was examined, revealing intriguing patterns. It was described that the parasites *Pomphorhynchus laevis* and *Gyrodactylus latus* significantly affected males, whereas the parasitic infection caused by *Asymphylogdora immitans* had a higher prevalence in females in this fish species (Aydogdu et al. 2014).

Likewise, some parasites exclusively affect one sex and are potentially related to the specificity of a tissue or organ. For example, *Kudoa ovivora* targets female gonads of a variety of fish including slippery dick (*Halichoeres bivittatus*), yellowhead wrasse (*H. garnoti*), Blackear wrasse (*H. poeyi*), and bluehead (*Thalassoma bifasciatum*) (Swearer and Robertson 1999). On the male side, some parasitic infections are also exclusive to this sex. As previously mentioned, a prime example is *Sphaerospora testicularis*, which has only been reported in male European sea bass (*Dicentrarchus labrax*) (Sitja-bobadilla and Alvarez-pellitero 1990; Castro et al. 2018). Some parasitic

infections, such as certain trematodes and monogeneans, have a higher prevalence in male fish due to their reproductive behaviors, which can involve aggressive interactions and territorial disputes (Poulin 2013). Meanwhile, in African sharp-tooth catfish (*Clarias gariepinus*) fish, the rate of prevalence of parasites and the intensity of the infection was higher in females (Amos et al. 2018). In fact, *C. gariepinus* together with Redbelly Tilapia (*Tilapia zillii*) presented slightly more infected females than males by helminths although the difference was not significant (Mgbemena et al. 2020). In pelagic Baltic herring (*Clupea harengus membras*), more males (and more intensively) were infected by the helminth *Anisakis simplex* (Podolska and Horbowy 2003). In contrast, taxa such as Myxozoa and Ciliophora presented higher prevalence in female goldfish (*Carassius auratus*) and Nile tilapia (Saha et al. 2015).

Viral infections

Kortet et al. (2002) found that the papillomavirus exhibited higher prevalence in males in the common roach (*Rutilus rutilus*), showing papilloma tumors in their bodies. Nevertheless, other viral agents causing viral hemorrhagic septicemia (VHS) and infectious hematopoietic necrosis (IHN) in rainbow trout (*Oncorhynchus mykiss*) did not typically show significant differences in prevalence between male and female fish (Amend 1975; St-Hilaire et al. 2002). It is worth mentioning that female zebrafish infected with SVCV exhibited lower antiviral response thanks to higher expression of the gonadal aromatase gene, *cyp19a1a* (Lu et al. 2022); however, the molecular mechanisms involved are not elucidated.

In 1996, Vethaak & Jol conducted an insightful investigation involving the flounder species *Platichthys flesus* aiming to establish a connection between environmental stressors and the prevalence of lymphocystis, a skin viral infection. While contamination levels were similar between both sexes, large and older males exhibited a notable increase in the occurrence of the viral disease. The heightened prevalence of lymphocystis in male flounder, in contrast to females, was potentially attributed to the stress associated with the spawning process.

Bacterial infections

The emergence and progression of diseases in fish are intricately tied to their environment. Research has demonstrated that specific bacterial diseases, which

are proven to be lethal to fish reared in captivity, do not exhibit the same impact on wild populations of the same species. A plethora of bacterial diseases in fish have been identified, leading to economic losses (Toranzo et al. 2005). Although many publications were found on bacterial infections in fish, only two considered sex as a factor to express in the data revealing the lack of integration of sex in the studies.

The effects of cumulative stressors affect the infection development and the pattern of the immune response, such as in Coho salmon females, in which exposure to thermal stress and high manipulation produced 28% more mortality than in males (Teffer et al. 2019). After one week, females showed physiological dysfunction as a result of both stressors while the relationship between infection levels and the regulation of immune genes was lower in females compared to males (Teffer et al. 2019).

The causative agent of furunculosis, *Aeromonas salmonicida*, and *Renibacterium salmoninarum*, responsible for bacterial kidney disease (BKD) were found in a prevalence of 15% and 25%, respectively (Loch et al. 2012). Both infections exhibited a notably higher prevalence among females in various organs, including the kidney and spleen of chinook salmon, *Oncorhynchus tshawytscha*, ($N=480$) during a study conducted in Michigan Lake (Loch et al. 2012). This investigation encompassed the assessment of ten different bacterial genera, yet *A. salmonicida* and *R. salmoninarum* were the most frequently identified. The analysis revealed significant interactions between the collection location/time and sex concerning these infections, particularly during the spawning season. In contrast, Amal et al. (2018) indicated that the susceptibility of Japanese medaka, *Oryzias latipes*, to *Streptococcus agalactiae* infection was not influenced by their sex, evident in the differences in the infection patterns among hosts and bacterial species.

The role of epigenetics in the sexual immune dimorphism

Sexual dimorphic phenotype is the result of a confluence of molecular mechanisms that interact during development. Sex-biased gene expression and the regulatory mechanisms involved have implications beyond evolution due to their predominant appearance in one of the sexes (Ellegren and Parsch 2007). Nonetheless, it remains to be determined whether sex-based differences in the expression of genes are caused by differential selection pressures acting in each sex, hormone-dependent effects, epigenetic mechanisms, or gene networks (Jaillon et al. 2019).

In humans, sex is an important determinant of the immune response, and women and men have different susceptibilities to diseases. These human sexual dimorphic responses have been attributed to epigenetic mechanisms, but the underlying determinants are far from clear (Klein and Flanagan 2016). It is known that differences in the immune activity between women and men are explained by the fact that a large number of immune system genes are located on the sexual chromosome X. For example, GPR174—an X-chromosome-encoded G-protein-coupled receptor—suppresses the formation of germinal centers in male, but not female, mice (Zhao et al. 2020). On this sexual chromosome, the epigenetic mechanisms can explain the sexual differences in the dosage compensation achieved through X-chromosome inactivation (XCI) between women (XX) and men (XY) (Chow et al. 2005). The X-linked X-inactive specific transcript (*Xist*) long noncoding RNA is indispensable for XCI and some X-linked genes escape silencing and remain expressed from both chromosome pairs in women (Netea et al. 2020). This concerns 12–20% of human X-linked genes (Loda and Heard 2019). Consequently, women have a more active immune system against pathogens but in contrast, makes women more sensitive to autoimmune diseases (Mauvais-Jarvis et al. 2020).

There is less data on the correlation of sex with diseases and on the epigenetic responses related to sex and the immune system. Although female fish are generally thought to be more robust than males, aquaculture practices should also consider the role that maternal stress has on the immune function of the offspring (Campbell et al. 2021), because underlying epigenetic mechanisms in the maternal inheritance have been described in fish (Pierron et al. 2021). Transgenerational immunity affects both innate and adaptive immune responses in teleost, as evidenced by the transfer of antibodies by fish females to eggs (Roth et al. 2018). This immune priming has also been observed in pipefish (*Syngnathus typhle*) progeny following bacterial treatments administered to both male and female parental and grandparental generations (Menon and Kumar 2016; Beemelmanns and Roth 2017). Further, Atlantic salmon embryos exposed to LPS displayed alterations in the methylome and transcriptome in adulthood, suggesting the possibility of epigenetic inheritance (Uren Webster et al. 2018). Parasitic transmission of *P. neurophilia* exposure occurs through both horizontal and vertical routes, with the latter involving the transmission of parasites through female oocytes (Sanders et al. 2013) therefore, although still not described, investigating potential

heritable epigenetic changes is crucial for controlling the disease outspread.

Clear sexual dimorphism in the DNA methylation levels of two innate immune genes (*IL1 β* and *Casp9*) has been detected in the zebrafish gonads, being significantly higher in testes when compared to ovaries (Caballero-Huertas et al. 2020). During zebrafish gonadal development, the undifferentiated gonad first develops as an ovarian-like organ, while half of the population develops testicular tissue through the activation of apoptotic pathways (Liew and Orbán 2014). By contrast, the nuclear factor kappa beta (*Nf-k β*) promotes cell survival by blocking apoptotic pathways and contributing to ovary development (Orbán et al. 2009). In this context, after larval immune stimulation, an alteration of the DNA methylation levels was found in two relevant innate immune genes, i.e., caspase 9 (*Casp9*) and interleukin 1 beta (*IL1 β*) (Moraleta-Prados et al. 2021), highlighting the interactions between the environment, the epigenetic events, and the immune system in the gonadal development. The activity of the immune system during gonadal development has been described in some fish species. For example, in turbot (*Scophthalmus maximus*), a transcriptomic analysis during sex differentiation revealed the expression of several genes related to the immune system such as *casp8* (Ribas et al. 2016). Similar observations were described in other fish species: European sea bass (Ribas et al. 2019), zebrafish (Ribas et al. 2017a), and sea bream (Chaves-Pozo et al. 2008). Sexual differences in the immune genes expressions have been also described in fish, such as the higher expression of cytokine signaling SOCS-3 in male yellow perch (*Perca flavescens*) after lipopolysaccharide injection (Shepherd et al. 2012), the differential transcriptomes related to sex steroids and immunity in the skin of males and females in spinyhead croaker (*Collichthys lucidus*) (Zhou et al. 2023), and the higher expression of gonadal aromatase gene (*cyp19a1a*) in female zebrafish, led to a weaker antiviral response compared to males after infections (Lu et al. 2022). Even though differences among the sexes are evident, the studies agreed that underlying genetic and epigenetic mechanisms are far to be understood and should be wisely explored.

Adjusting fish management to sexual dimorphism in the immune system

Aquaculture currently provides ~53% of fish consumption compared to fisheries, and it is estimated that by 2050, there will not be enough fish to supply global

demand (Food and Agriculture Organization, FAO 2018). Farm animals intended for human consumption are raised in artificial environments that are very different from the conditions found in nature. These environmental differences have a relevant impact on many aspects of the biology of these cultivated animals, especially in early development, altering the final phenotype (Skinner et al. 2010). A major and frequent problem for aquaculture is fish disease outbreaks which can cause serious economic losses due to high morbidity and/or mortality. The main cause of these epidemic events is usually high breeding densities, a common practice in intensive aquaculture that maximizes the use of space facilitates the transfer and spread of pathogens. Thus, on-farm biosecurity measures to exclude pathogens and minimize health risks are commonly employed in intensive and super-intensive systems (Walker and Winton 2010).

The crucial role of stress in modulating the immune system has been discussed, as it often reduces the effectiveness of immune defenses against diseases (Tort 2011). In the context of breeding and maintenance of fish species in captivity, many factors come together and can affect the physiological systems of cultured individuals. On one hand, it is usual that male fish display aggressive behavior toward other males, experiencing greater levels of cortisol when exposed to stressors in comparison to females (Chow et al. 2016; Caballero-Huertas et al. 2021). Balancing the number of males and females in tanks, or even increasing that of females could lead to lower levels of stress in the tank compared to one with a high number of males (Ribas et al. 2017b, Caballero-Huertas et al. 2021).

According to the One Health approach (which recognizes the interconnection between people, animals, plants, and their shared environment), it is crucial the investment in efficient and sustainable animal culturing in which disease outbreaks should be avoided, limiting the use of antibiotics or other sources of risk dumping in the water. This strategy should connect human health, environmental water quality, farmed organism health and welfare, and biodiversity, and must be urgently applied in the current scenario of aquaculture production (Cavalli et al. 2015; Stentiford et al. 2020; Gozlan et al. 2003), which faces great challenges such as increasing demand and the impact of climate change. An alternative to antibiotics to control infectious diseases is vaccination since the use of antimicrobial agents in aquaculture has resulted in the emergence of reservoirs of antimicrobial-resistant bacteria in fish and other aquatic animals as well as in the environment (Heuer

et al. 2009). Nevertheless, major limitations in fish vaccine development are the still little knowledge of fish immunology, the restriction in the type of pathogen they combat (mainly economically important bacteria), many vaccines unlicensed, not cost-effective (expensive), and the stressful administration in many cases (Muktar et al. 2016). To counter some of these problems, autogenous (auto)vaccines are customized vaccines developed from pathogens isolated directly from affected production facilities where the vaccines are subsequently applied under a minor use or restricted permit (Barnes et al. 2022). Moreover, the incidence of some infectious diseases, especially in the tropics, may increase with climate change (Leung and Bates 2013), so protective therapies must be developed quickly and effectively, minimizing long licensing terms. Other prevention approach is the stimulation of the immune system with feed additives and the use of therapeutants, a far-reaching practice in fish production (Lieke et al. 2021).

Furthermore, it is here where the concept of protection against infections is introduced through the breeding selection (e.g., marker-assisted selection, Griot et al. 2021; genomic selection, Palaikostas et al. 2018) or manipulation of resistant genomes, but also of potential epigenetic therapies that go along this line. Genome editing technique CRISPR/Cas9 (clustered regularly interspaced short palindromic repeats/CRISPR-associated protein 9) has been used on different salmon species, farmed carp (*Labeo rohita*), channel catfish (*Ictalurus punctatus*), and grass carp (*Ctenopharyngodon idella*) for targeting disease resistance, inserting transgenes, or editing of disease resistance genes (Ma et al. 2018; Okoli et al. 2022). In 2022 in Japan, under a sustainability measure, transgenic by CRISPR/Cas9 was governmentally approved to produce fugu red sea bream and tiger puffer fish with higher growth performance (Japan embraces CRISPR-edited fish 2022). On the contrary, currently, no Genetic Modified (GM) animals or derived products are on the EU market, despite the fact that scientific developments suggest submissions may be made in the future across a range of species (EFSA 2023). Thus, investments to improve fish production should be made toward biotechnology but also to better understand sexual dimorphism in the (epi) genetic response of the immune system.

Promoting cutting-edge biotechnologies will contribute to the development of innovative breeding protocols, which will have a significant influence on research in the field of aquaculture and aid in unraveling the intricacies of interactions involving sex and immunity. The industry might exploit the use of epimarkers that can

identify infected fish or the most resilient to infections and decipher if sex is a relevant factor to be considered for disease therapies. This research direction will generate novel breeding protocols based on sustainability and will generate patents impacting the European and international economies. Sustainability is integrated as a Blue Economy mission in the Oceans Horizon Europe (Mission Starfish 2030, Target 2 and 12, European Union) and in the Sustainable Developmental Goal 2 (SDG2) to End Hunger (United Nations).

The resulting knowledge can help improving fish productivity while ameliorating and making the application of the European legislation more effective on using animals for scientific purposes through animal associations like FELASA. Directive 2010/63/EU (EU 2010) on the protection of animals used for scientific purposes deals imprecisely with animal sex, as it uses the word “gender” while “sex” does not appear in the “Severity classification procedures” section. Nonetheless, intending to research infectious treatments for the direct application in underwater animals, the Aquatic Animal Health Code – 29/08/2019 of the World Organization for Animal Health (<https://aquaculture.ec.europa.eu/knowledge-base/guidelines/aquatic-animal-health-code>) considers sex (among others factors such as host characteristics, vectors, immune status, genetic resistance, and age) as a critical element of surveillance of the epidemiological unit. In this sense, the relevant epidemiological unit for the surveillance system should be defined and documented to ensure that it is representative of the population or targeted subpopulations that would generate the most useful inferences about disease patterns (Article 1.4.3. – Aquatic Animal Health Code). Thus, sex may play a main role in policy-makers to better interpret disease development, symptoms, and response of the immune system.

In conclusion, based on the directives and programs developed in recent decades, this review, particularly focused on teleost, showed that sex is a critical variable not only in human clinical trials but also in livestock and, specifically in aquaculture production. Nevertheless, studying sex as a central factor in fish to better understand the data is still far from being completed. It was observed a lack of specific regulations, and limited specifications, promoting the inclusion of sex in aquaculture research. This oversight may result in potential losses arising from emerging pathogens in fish stocks. Thus, it should be highlighted the need to consider sex as an essential factor in fish-related research because it will improve treatment strategies. Further, it is recalled the urgency of including sex for robust legislation to address research appropriately.

Disclosure statement

All authors declare that they have no competing interests and that the content of the present manuscript has not been published or is being submitted elsewhere.

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