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1    **Pathogens shape sex differences in mammalian aging**

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8

9    **KEYWORDS:** pathogen exposure; immunosenescence; lifespan; life history traits; medicine

10

11    **ABSTRACT**

12    Understanding the origin of sex differences in lifespan and aging patterns remains a salient  
13    challenge in both biogerontology and evolutionary biology. Different factors have been  
14    studied but the potential influence of pathogens has never been investigated. Sex differences  
15    especially in hormones and resource allocation generate a differential response to pathogens  
16    and thereby shape sex differences in lifespan or aging. We provide an integrative framework  
17    linking host pathogenic environment with both sex-specific selections on immune  
18    performance and mortality trajectories. We propose future directions to fill existing  
19    knowledge gaps about mechanisms that link sex differences, not only to exposition and  
20    sensitivity to pathogens, but also to mortality patterns, whilst emphasizing the urgent need to  
21    consider the role of sex in medicine.

## Sex differences in mammalian lifespan

In almost all human populations, and consistently throughout history, women live longer than men [1]. This pattern is pervasive in mammals [2], although the difference in **lifespan** (see Glossary) between sexes varies strikingly across species and populations facing contrasted environmental conditions [2,3]. Currently, a large body of research is devoted to the understanding of evolutionary, genetic, and physiological mechanisms that govern these sex differences in lifespan [4,5]. Differences in life-history strategies between sexes driven by **sexual selection** are among the most common explanations [6]. However, evidence that sexual selection mostly shapes sex differences in lifespan remains equivocal [2]. Here, we highlight that sexual selection, by selecting for traits and behaviors that increase male reproductive success, also leads males to be more exposed to **pathogens** than females. Moreover, earlier **aging** of the immune system can occur in males. This can lead to sex differences in aging, which can be exacerbated in pathogen-rich environments.

Up to now, the literature on the deleterious consequences of infectious diseases has focused on the deterioration of the immune system with increasing age (i.e. the **immunosenescence** process; Box 1). In humans and wild vertebrate populations, aging of the **adaptive immune system** may occur earlier in males [7,8]. These different patterns of immunosenescence could occur between sexes due to a variety of interactions between physiological factors and the local environmental context. For instance, more intense stimulation of immune defenses through a greater pathogen exposure could contribute to earlier aging of the male immune system, leading to an earlier onset of their **actuarial senescence**. In support, HIV-1-infected individuals experience immunologic changes similar to uninfected elderly persons as a result of the continuous stimulation of their immune system [9]. However, the contribution of immunosenescence to the observed sex differences in lifespan and aging within and across mammals is yet to be deciphered. We argue that sex-specific immune responses and sex

differences in energy allocation strategies driven by sexual selection, by leading to differences in both exposure and susceptibility to pathogens, should result in an accelerated immunosenescence in males through immune exhaustion. If this hypothesis is correct, sex differences in lifespan, through either direct (host mortality) or indirect (faster immunosenescence) effects, could be modulated according to the pathogenic environment of populations [2] (Figure 1) and have direct consequences in human as well as veterinarian medicine (Box 2). Although the sample size was limited, a preliminary analysis of currently available data supports this hypothesis with sex differences of lifespan increasing in favor of females when pathogen richness increases (Box 3).

## **How biological differences between males and females contribute to disease dimorphism?**

As a general rule, **prevalence**, **intensity**, and **pathogenesis** of infections caused by diverse pathogens (i.e. viruses, bacteria, parasites, and fungi) are higher in males than in females in humans, domesticated animals, companion animals, laboratory rodents, and numerous species in the wild (see review in [10]). For example, in adult mice (*Mus musculus*) males display more symptoms of sickness than females when they are exposed to bacteria that cause an illness with symptoms similar to the flu [11]. Women have more than 40% less HIV-1 RNA loads than men [12], while Italian men infected by the SARS-CoV-2 are approximately twice more likely to die than infected women [13]. Beyond obvious morphological, anatomical, and behavioral differences (e.g. aggressiveness) that might affect exposure to pathogens, many other biological differences may contribute to observed sex differences in the susceptibility or disease progression [14]. Yet these differences remain little studied and data on the underlying biological mechanisms are surprisingly scarce, while they lead to different responsiveness to treatment between sexes [14] (see Box 2).

71    *Sex, hormones and immunity*

72    It has become increasingly clear that males and females differ in immune responses [15]. As a  
73    general rule, females exhibit greater capability of producing antibodies than males [16]. They  
74    are less susceptible to infectious diseases [15] but can develop a stronger predisposition to  
75    autoimmune or inflammatory diseases than males [15]. However, the consequences in terms  
76    of sex differences in lifespan and aging are yet to be accurately quantified [17].

77    Differences in disease prevalence and expression between males and females are mainly  
78    attributed to sex steroids (e.g. estrogens, testosterone, progesterone), which, by binding to  
79    hormone receptors on the surface of immune cells, modulate the phenotype of immunological  
80    cells [7,15]. Most of them express multiple sex hormone receptors that drive sex-specific  
81    immune responses following antigen stimulation [7]. Males and females differ in steroid  
82    concentrations: males have a higher concentration of testosterone and females a greater  
83    concentration of estrogen and progesterone. Estrogen receptors are detected in immune cell  
84    populations, including lymphocytes, monocytes and macrophages [18], and have an immuno-  
85    enhancing effect as well as diverse protective effects [19]. On the contrary, progesterone and  
86    testosterone have mainly immunosuppressive effects [20]. Folstad and Karter [21] proposed  
87    that testosterone has, in fact, a double-sword effect that increases the probability of mating for  
88    a male while decreasing its ability to fight over pathogens. For instance, territorial male  
89    chamois (*Rupicapra rupicapra*) have almost six times more fecal androgen metabolites and  
90    are three times more parasitized during the rut period than non-territorial males [22]. Hence,  
91    we may expect that males will develop stronger disease symptoms resulting in a lower  
92    probability to survive and thereby increased between-sex differences of lifespan in pathogen-  
93    rich environments. However, inconsistencies among studies of vertebrate species (e.g. Cape  
94    ground squirrels, *Xerus inauris* [23]) suggest that testosterone is not all story.

## 95 *Immune system and reproduction*

96 Major physiological changes occur during reproductive seasons or cycles. Typically,  
97 testosterone production is increased in males when competing for fecund females, while  
98 pregnancy induces a decrease in estrogen and an increase in progesterone concentration to  
99 avoid the immunologic aggression of the fetus [24]. However, infectious diseases that are  
100 acquired during pregnancy or lactation are often associated with lower birth mass and reduced  
101 breast-milk in humans, suggesting that females reactivate the formally quiescent immune  
102 system [25] to combat infection at the expense of reproduction. For example, women who  
103 contract malaria during pregnancy have higher circulating levels of pro-inflammatory  
104 cytokines, which in turn are associated with lower birth mass [26]. This suggests that females  
105 should show a lower **lifetime reproductive success** in an environment with high pathogenetic  
106 load, but their lifespan should be much less affected than that of males.

## 107 **The evolutionary roots of sex differences in response to pathogens**

108 From an evolutionary viewpoint, the immune response is a key fitness-related trait, but the  
109 energy it requires should inevitably be traded for allocation to life-history traits governing  
110 other biological functions [27]. For instance, the growth and maintenance of secondary sexual  
111 traits impair male immune performance through a resource-based allocation trade-off [28],  
112 making them more sensitive to pathogens [29] (Figure 1). Many observations in rodents,  
113 birds, and insects document substantial energetic, reproductive, and survival costs of immune  
114 activation [30]. Hence, organismal responses to pathogens should involve sex differences  
115 given that the optimal solution to the trade-off between reproduction and survival differs  
116 between sexes, with females allocating more than males to their immune responses to not  
117 jeopardize their survival and increase thereby their lifetime reproductive success [27]. We can  
118 even expect that iteroparous females should rapidly redirect their energy to immune functions

at the expense of fetus/offspring survival when exposed to a pathogen during pregnancy. The optimal strategy should be radically different in semelparous females who only have one opportunity to reproduce. For example, parasite removal reduces reproducing female survival in the Taiwan field mouse (*Apodemus semotus*), possibly by allowing breeding females to increase maternal investment (i.e. allocation at the cost of their future survival [31]). By contrast, in males, immune performance is impaired by the growth and maintenance of secondary sexual traits, which makes them more sensitive to pathogens [28]. In mice, increased aggression is costly and is associated with reduced resistance to disease [32]. As a consequence, sex differences of lifespan should increase in favor of females when pathogen load increases (Box 3).

Finally, males and females correspond to markedly different environments for pathogens, which may shape their evolution. Hence, the observed sex-biased disease prevalence and/or severity might be the result of the parasite having adapted to grow in specific host sex [33]. Úbeda and Jansen [34] formalized this idea and suggested that natural selection can act differently on pathogens in males and females depending on the transmission route of the pathogen. In Japan, where the transmission of HTLV-1 (Human T-cell Lymphotropic Virus Type 1) occurs through breast-feeding rather than through sexual transmission, the progression to Adult T-cell Leukemia is slower in women than men. Sex-specific adaptation of HTLV-1 to preserve women as a viral route could be a potential explanation for this puzzling observation [34].

**The need to consider sex-specific immune performance and pathogen exposure in evolutionary biology**

*Challenges within species*

The immune system includes many different immune cell types, each having its unique function, and collectively protecting the host against pathogens. The reliable measurement of multiple markers of both immunity (e.g. cellular components, T cell repertoire) and aging (e.g. epigenetic markers of biological age [35]) remains challenging. However, such metrics are required to allow a better understanding of the ecological (pathogen exposure) and evolutionary forces that shape the sex-specific decline of immune responses and between-sex differences in lifespan. Ideally, these measures should be made in wild populations, which display a large variation in the magnitude of sex differences in lifespan (see [2]) because of differential risk-taking behavior, food requirements, mortality due to direct sexual competition, or exposition to commensal and pathogenic organisms. Longitudinal studies are thus required to assess how immunosenescence patterns are shaped according to sex (see for example [36], and references in [8]) and also to identify mortality causes, which allows deciphering the different ways through which pathogens reduce individuals' lifespan (through early deaths from lethal diseases or through advanced immunosenescence due to immune exhaustion). This has yet rarely been investigated in wild populations (but see [37]).

Even though studies of rodents (reviewed in [38]) show that reaching this aim is possible in wild populations, it remains a complex task. Populations living in protected conditions (e.g. wild species in zoos, domestic animals and companion animals living with humans, laboratory animals) would offer excellent simplified systems to explore more deeply the deterioration of immune functions with increasing age and its role in between-sex mortality patterns (see [39] for an example in mice). This would allow an investigation into how the level of pathogen exposure as well as the virulence of pathogens to which hosts are exposed shape the immunosenescence profile and thus the mortality rate and lifespan of males and females.



Captive mammalian populations could also provide insightful information on the potential effect of chronic and putatively asymptomatic infections on the differential rates of immunosenescence between sexes, which is currently totally underestimated. Research on human health has provided important and somewhat unexpected results in this field. Notably, the chronic infection by the common CMV (cytomegalovirus) is involved in the remodeling of the immune system. Hence chronic exposition to any microbial agent (i.e. not only known pathogens) could be both implied in shaping sex-specific immunosenescence [40]. Only long-term monitoring of individuals from birth to death, in which molecular and cellular markers of adaptive and innate functions can be recorded repeatedly throughout their lifetime, and a reliable estimate of the infection date becomes available at the individual level, will allow a deeper understanding of immunosenescence according to age and sex concerning microbial agent exposure.

Additionally, the comparative analysis of populations within a single species occupying multiple habitat types can offer important insights into the intraspecific variation in immunosenescence and its consequences on life history traits such as lifespan in both sexes. Selection is expected to produce the immune response that maximizes individual fitness, in interaction with other selection pressures imposed by the environmental context (i.e. resource availability, weather conditions), the social and mating systems, and the pathogen exposure. Thus, the immune system of rodents from different populations and environments in the wild differs from that of laboratory rodents, the former being continuously exposed to commensal and pathogenic organisms (reviewed in [38]). It would be thus interesting to evaluate how such excessive energetic demands to activate the immune system compromise other fitness components of laboratory rodents according to their pathogenic environment, notably the differential actuarial senescence rates between males and females.

*Inter-specific comparisons*

Taking into account the evolutionary history of mammals, their pathogen species richness, which varies largely across species [41], may help explain between-sex differences in lifespan. In presence of numerous pathogens, males from species subjected to strong sexual selection should be more exposed to pathogens compared to females than males from species with a low sexual selection [42]. This could partly explain sex differences in immunosenescence (see for example [8]) and highlight how these differences are likely determined by fine scale interactions between sex-specific physiological pathways and the local environment in pathogens [2].

Variation in pathogen richness, infection rate, and pathogen load correlates with numerous morphological and ecological traits, mostly driven by sexual selection, which are also related to the lifespan variation in mammals [43]. Among these traits, variation in host body size [44], mating system and sexual size dimorphism [42], MHC allelic diversity [45], geographical range [46], social group size [47], population density [48], and phylogeny [6,41] have been identified as playing a role. However, most cross-species studies that investigate the interaction between pathogens and host ecological and life-history traits performed to date did not include between-sex differences in pathogens nor their consequences in terms of sex-specific lifespan (e.g. [49]). Although male-biased parasitism is positively correlated with the level of polygyny in mammals [42], the level of polygyny also correlates with a shorter lifespan and a more pronounced aging in males compared to females, at least across captive populations of large herbivores [6].

All these challenges will be made possible thanks to databases gathering longitudinal data that measure accurately sex differences in lifespan, which are becoming increasingly available (e.g. [2]). Besides, several databases recording the number of pathogen species found in mammals, such as the World Register of Marine Species [50], Pathogen-Host Interactions (Phi-Base) [51] or the Database of Bat-associated Viruses (DBatVir) [52] have been

developed. These databases provide a large amount of information about the diversity and the richness of parasites across mammalian species displaying contrasted life styles. Combining these databases should allow better understanding the role of pathogens in between-sex differences of lifespan and aging (e.g. in terms of both onset and rate of actuarial and/or **reproductive senescence** patterns) across mammalian species (see Box 3). In our view, this information should inform on how pathogens shape sex differences rather than how sex differences shape responses to pathogens because the magnitude of sex differences seems to be context-specific (see [2] for a study of mortality patterns). It might be thus difficult to envision mammals evolving differential responses to parasites mediated by sex differences if the magnitude of sex differences is so labile.

## **Concluding remark**

Understanding the determinants of differences in male and female outcomes is becoming a crucial recognized challenge in infectious disease research in humans as well as in veterinary clinical research, such as identifying the true contribution of pathogens to overall mammalian mortality (see Outstanding Questions). Available information so far calls for an appropriate inclusion of sex differences over the whole human life span to anchor medicine in the real word (see Box 2). Longitudinal studies combining detailed immunological and non-immunological follow-ups for individuals of each sex should help to understand aging of the immune processes and how it differs between sexes and environments (see Outstanding Questions). By taking into account the evolutionary history of mammalian species, such a holistic approach could help explain between-sex differences in lifespan. For instance, studies should focus on consequences of resistance and tolerance of pathogens on lifespan across mammals (see Outstanding Questions). We encourage the scientific community to adopt this holistic approach, which is necessary to embrace all the methodological, theoretical and

conceptual challenges raised by pathogens regarding sex differences in lifespan. The increasing availability of required data offers great opportunities to formulate and test new hypotheses.

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374 GLOSSARY

375 **Adaptive immune system:** antigen-specific immune responses characterized by  
376 immunological memory that makes future responses against a specific antigen more efficient.

377 **Aging:** decline in the age-specific contribution to fitness throughout life. As a consequence,  
378 the aging process is mostly studied in the two main fitness components: survival and  
379 reproduction. Survival ageing (also called **actuarial senescence**) corresponds to the decrease  
380 in survival rates with increasing age and reproductive ageing (also called **reproductive**  
381 **senescence**) corresponds to the decrease in reproductive rates with increasing age.

382 **Immunosenescence:** decline of immune parameters with increasing age, associated with  
383 detrimental clinical outcome (e.g. high risk of contracting and dying from infectious diseases).

384 **Intensity of infection:** pathogen load within an individual at a given time.

385 **Lifetime reproductive success:** number of offspring alive produced by an individual at some  
386 life stage (usually birth, weaning, or one year of age) during its entire lifetime.

387 **Lifespan:** time interval between the birth and the death of a given individual.

388 **Pathogens:** organisms that cause disease to the host. They include in particular ectoparasites,  
389 protozoan, helminths, virus, bacteria and fungi.

390 **Pathogenesis:** progression of the disease. It encompasses the complete sequence of events  
391 accompanying acute and persistent infections.

392 **Prevalence:** proportion of infected individuals within a population at a given time, which  
393 encompasses both old and new cases.

394 **Sexual selection:** evolutionary process arising either through mating choice (i.e. preference  
395 by one sex for certain characteristics (e.g. form, color, or behavior) in individuals of the other  
396 sex) or through intra-sex competition (i.e. competition among mature individuals of one sex to  
397 monopolize access to mate with individuals of the other sex). Both ways select for a large  
398 sexually size dimorphism and extravagant sexually secondary characters such as ornaments or  
399 weapons when sexual selection is strong.



## **Box 1. Sex-specific immunosenescence**

A decline in immune defense with increasing age, defining the immunosenescence process, has been highlighted in numerous species across the tree of life [8]. However, the few results available so far do not support that a sex difference of immunosenescence pattern would cause the observed sex differences of adult mortality [8,36].

Progressive deterioration of the organism results from concomitant retention (or exacerbation) of innate immunity coupled with a dysregulation (or dysfunction) of adaptive immunity [53]. For now, in all studies conducted so far in humans, a universal age-associated immune alteration is consistently observed. The numbers and proportions of naive peripheral blood CD8+ T cells are reduced as a consequence of the developmentally-programmed thymic involution [53]. Moreover, as the establishment of the innate immune response causes inflammation and ROS production that induce collateral tissue damage, we can hypothesize that the more an organism is subject to a repeated innate immune response (e.g. due to high exposure to pathogens), the more permanent the damage will be. This potentially accelerates an organism's deterioration, ultimately leading to its death. Similarly, the adaptive immune system is particularly affected by the effect of long-term exposure to a variety of antigenic stimuli. Accordingly, an adaptive immune system highly exposed to pathogens will quickly lose efficiency, leading it to exhaustion with dramatic consequences such as high mortality.

As increased solicitation of the immune system leads to an acceleration of its dysregulation and efficiency, we suggest that in presence of pathogens, males undergo stronger immunosenescence than females, because of their higher exposure and tolerance to infectious agents. This results in the observed higher mortality rate and shorter lifespan of males compared to females. For example, Zeng et al. [54] highlighted that two immune pathways, the cytokine IL-6 and TLR3 proinflammatory signaling pathways, are positively associated

424 with the lifespan of centenarian men but not women. This suggests that dysregulation of these  
425 proinflammatory pathways with age makes elderly men more susceptible to infectious  
426 pathogens than elderly women. However, while numerous researchers asked for more  
427 longitudinal studies to define more accurately immunosenescence profiles and identify the  
428 underlining mechanisms [53], sex remains overlooked in biological research despite its  
429 critical consequences in the veterinarian and human medicine.

## **Box 2. The urgent need to consider sex in medicine**

Investigating the role of pathogens on sex differences in aging highlighted how much males and females differ regarding their immune system and their response to infectious diseases. In spite of this, physicians still tend to prescribe the same treatment to both male and female patients for a given diagnostic. One reason for this is that sex differences in immune functions are not well understood yet.

During the last thirty years, most biomedical research has routinely used only males in both cohort and animal model studies because the cyclic hormonal fluctuations of females introduce additional experimental variation [55]. This could explain the higher number of secondary effects observed in women than in men following the commercialization of a given drug [56]. Upon vaccination, women develop a higher antibody immune response, but also more frequent and severe adverse side effects than men [57]. The application of sex-specific medicine is thus urgently required [56]. The American National Institute of Health recently declared that clinical trials not taking sex-specific responses into account will no longer be funded [58].

A great deal of knowledge about sex differences in immune functions comes from laboratory animals, notably the mouse model, which have been used extensively to develop research and test therapies before they are used in humans. However, very little is known about how much information from inbred and laboratory-adapted mice can be extrapolated to mammalian immune responses in the wild [59]. First, the selection of laboratory mice has resulted in the alteration of life-history traits (such as reproduction or lifespan, see [60]) and immunological traits of individuals. Second, as argued above, animals' immune responses are just one dimension of a wider life-history strategy to maximize fitness within the constraints of the environmental context. Laboratory conditions strongly differ from the environment

454 individuals face in the wild, which can have serious consequences on the immune response  
455 they mount. Comparison between male and female immune functions in wild and laboratory  
456 animals is thus crucially needed to reveal both the relevance and limitations of laboratory  
457 animals as immunological models. Linking wild and laboratory animal immunology by using  
458 tools and concepts of immunology, but also of ecology and evolutionary biology, is badly  
459 needed. In that respect, companion animals, which live in the same environment as their  
460 owners and are exposed to similar pathogens [61], may potentially serve as bridges between  
461 laboratory and wild species. The affordability of new ‘omic’ approaches and the availability  
462 of new trusted biomarkers (e.g. antibodies, cytokines, cellular responses) and immunological  
463 reagents (e.g. monoclonal antibodies) will help to quantify male and female exposition to  
464 microbes and the dysregulation of immune parameters with increasing age in a wider range of  
465 mammalian species, aiding immunologists, ecologists and evolutionary biologists to work  
466 altogether.

**Box 3. Relationship between sex differences in mean adult lifespan and increased pathogen richness**

Using between-sex differences of mean adult lifespan in 13 mammalian species (8 carnivores and 5 primates, see more details in supplemental Table S1), a preliminary analysis (Figure I) reveals that between-sex differences of lifespan increases ( $0.335 \pm 0.139$ ,  $p = 0.03$ ) in favor of females when pathogen richness increases. The mean adult lifespan for the 13 species was obtained from [2]. Pathogen richness is defined as the cumulative number of pathogen species inventoried (arthropods, helminths, protozoans, virus, and bacteria) for each carnivore and primate species, males and females combined (extracted from literature and standardized for a given sampling effort). Linear models have been fitted with between-sex differences of mean adult lifespan as the response variable, and pathogen richness and ‘family’ (Carnivora or Primates as factors) as explanatory variables. For each species considered, the number of studies inventorying one or several pathogen species was recorded as an indication of the sampling effort exerted on the species and included in the analysis: pathogen richness values correspond to the residuals of the linear model with real pathogen richness in response variable and the sampling effort as an explanatory variable.

**Figure I. Increase of sex differences of mean adult lifespan in favor of females when pathogen richness increases for 8 carnivore (full circle) and 5 primate (open circle) species.**

488 **Figure legend**

489 **Figure 1. Different selective strength between sexes driving the evolution of sex**  
490 **differences.** These differences include those in life-history traits (blue boxes), in physiology  
491 and the immune response to pathogens (yellow boxes), and in aging and lifespan (red boxes).  
492

