Review article

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The conneXion between sex and immune responses

In the format provided by the authors and unedited

	Pathogen	Pathogen prevalence and incidence	Pathogen load and disease severity	Mouse models & mechanisms/pathways of sex
	.		-	bias
	SARS-CoV-1, SARS-CoV-2	Higher incidence of infection in males ¹⁻¹⁰	Adult males (45-79yrs) have higher mortality for SARS-CoV1 and 2 ^{5,6 9} Females infected with SARS-CoV2are more likely to be diagnosed with Long Covid ^{11,12}	Male mice are more susceptible to SARS-CoV infection ¹³⁻¹⁵ Male mice infected with SARS- CoV have increased accumulation of inflammatory macrophages and neutrophils in the lung ^{3,13} Estrogen receptor signaling is protective after SARS-CoV- infection ^{13,16} The SARS-CoV-2 entry receptor ACE2 is biallelically expressed in females, and may contribute to sex bias through regulation of viral entry and its function in the renin-angiotensin-aldosterone pathways ^{4,17}
VIRUS	Influenza Virus	Infant males and older adult males have increased incidence of infection ¹⁸⁻²³	Males (pre-pubescent or elderly) have higher mortality than females ^{19,23} Females are more likely to be symptomatic after infection and have a wider range of symptoms compared to males ²⁴ Females (ages 15- 49yrs) had higher mortality during the 1957-1958 H2N2 pandemic as well as after H5N1 infection ²⁵ Females (ages 20- 49yrs) had higher morbidity rates compared to their male counterparts during the 2009 H1N1 pandemic, whereas younger (<20yrs) and older (>80yrs) males had higher morbidity	Male mice are more resistant to influenza viruses than female mice, with female mice exhibiting lower LD50 values for mouse adapted H1N1 and H3N2 viral strains ²⁵ Sex differences in morbidity after infection with mouse-adapted influenza (H1N1, H3N2) are dose-dependent, where female mice have greater body mass loss, more hypothermia, and lower rates of survival than male mice at median doses ²⁹ Female mice have a greater level of protective immunity following influenza vaccination ^{30,31} Lower levels of testosterone in male mice correlate with poorer protection from influenza A virus ³²⁻³⁵ Estriol was shown to protect female mice from severe disease after infection of influenza A virus and decreases influenza viral replication ³⁶

		rates than similarly aged females ²⁵	
		Pregnancy is associated with worse outcomes from seasonal, outbreak, and pandemic influenza viral infections, and contributes to higher overall morbidity and mortality in females ^{18,26-28}	
Hepatitis A Virus	Males are more likely to be hospitalized ³⁷	Males have higher mortality ³⁷	n/a
Hepatitis C Virus	Similar incidence rates between males and females ³⁸	Males have greater disease severity (HCV-associated cirrhosis) ³⁸ Females are more likely to clear virus ³⁸	n/a
West Nile Virus	One case study shows a higher percentage of affected males ³⁹	Similar initial viremia in males and females ³⁹ A meta-analyses revealed that females report a higher diversity of symptoms ³⁹ Males have an altered cytokine response compared to females in the post-IgM phase, with elevated levels of CCL2, CCL11, IL-15, and CXCL10 ⁴⁰ Infected males have higher hospitalization rates and higher incidence of neuroinvasive disease and increased mortality ^{39,40}	n/a
Human Immunodeficiency Virus (HIV)	Females have higher incidence ⁴¹ Females have higher levels of immune activation and interferon	Females have lower viral loads in the early stages of infection, but comparable viral loads at the advanced stage ^{42,43}	Male-to-female transmission appears more efficient than female-to-male transmission ⁴⁴

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	signature gene expression ⁴²	No sex difference with regards to disease progression or clinical outcomes ^{42,43}	
Human cytomegalovirus (HCMV)	Females (post-puberty and pre-menopausal) have higher incidence of HCMV seroprevalence ⁴⁵	One study reported that HCMV infection suppressed reactivity to TLR2 and TLR7/8 stimulation in females but not males ⁴⁶	n/a
Herpes Simplex Virus (HSV)	Females have higher prevalence of HSV-2 (15.9% females) than males (8.2%) ^{47,48}	No sex differences with symptoms ^{47,48}	 Female mice are more susceptible to infection⁴⁹ Female mice have higher HSV titers in brain tissue⁴⁹ Higher mortality in male mice⁵⁰ Ovariectomy of female mice or estrogen treatment of male mice eliminated sex differences after infection⁴⁹ Sex-biased survival differences depend on type I IFN signaling and DAP12 signaling⁴⁹
Coxsackievirus	n/a	n/a	Male mice have increased mortality ^{49,51} Males develop more severe cardiac inflammation due to T _H 1 – skewed responses ⁵¹ Females are more resistant to infection and exhibit predominantly T _H 2-type responses ⁵¹
Ebola Virus		Males have higher mortality ⁵²	n/a
Measles Virus	At ages 45-64, females have a higher incidence ⁵³ , whereas at ages age 0-45, males have a higher incidence of infection ⁵⁴	Females (ages 0-49) have higher mortality, particularly post- puberty and pre- menopause ⁵³ .	n/a
Respiratory Syncytial Virus (RSV)	Males have higher incidence ^{55,56} , but a metanalysis of acute respiratory infections in Africa did not identify sex as a factor in RSV prevalence ⁵⁷	Males have higher rates of hospitalizations ⁵⁵	Male neonatal mice have higher viral gene expression after RSV infection, and delayed viral resolution ⁵⁸ After early-life RSV infection, male mice exposed to allergens have severe allergic exacerbation (female mice are protected). The TSLP pathway

		1	I	
				(which impacts IFN β production) alters male immune environment after neonatal infection ⁵⁸
	Heliobactor pylori	Males have greater <i>H.</i> <i>Pylori</i> sero- prevalence ^{59,60} After adjusting for age, males have 33% greater odds of infection. The prevalence of infection is 5% higher for males ⁵⁹	Males have more severe inflammation, atrophy, and intestinal metaplasia ⁶¹	Male mice are more susceptible to <i>H.pylori</i> infection Males have higher colonization levels for <i>babA</i> virualence factor of H. pylori ⁶² Male mice treated with estradiol produce less IFN γ and IL-1- β , and increased IL-10 and T _H 2 associated IgG1 levels ⁶² Estrogen is protective against gastric lesions; ovarectomy increases severity of gastritis and gastric cancer ⁶²
BACTERIA	Pseudomonas aeruginosa	Young females are more likely to be infected than young males ⁶³	Female patients with cystic fibrosis have worse disease prognosis upon infection compared to male patients with cystic fibrosis ⁶⁴	Female mice are more susceptible to infection ⁶⁵ Female mice mount strong inflammatory response in lungs ⁶⁵ Estradiol upregulates expression of secretory leucoprotease which inhibits TLR-dependent IL-8 release in bronchial epithelial cells during <i>P.aeruginosa</i> infection ⁶⁵
	Salmonella	Higher incidence rates of salmonellosis in males up to age 15 ⁶⁶ Females have higher incidence rates (ages 15– 64) ⁶⁶		n/a
	Chlamydia trachomatis; Chlamydia pneumoniae	Males have greater prevalence (<i>C.</i> <i>pneumoniae</i>) ⁶⁷ Females have higher prevalence (<i>C.</i> <i>trachomatis</i>) ⁶⁸	Males have higher levels of <i>C.</i> pneumoniae ⁶⁹ Females have higher infection rates because they are more likely to be screened (<i>C.trachomatis</i>) ⁷⁰ Estrogen levels correlate with chlamydial load ⁶⁹	n/a

		Chlorendia induced	
		Chlamydia-induced arthritis more common	
		in men ⁷¹	
	Males have higher	Males more likely to	n/a
	incidence ⁷²	develop Brucellosis ⁷³	11/a
Brucella spp.	Incidence		
Brucena spp.	No sex bias with regards		
	to prevalence ⁷²		
	Males have higher	Males have more	Male mice exhibit more evidence
	incidence (USA 1992-	hospitalizations and	of infection across tissues and
	1998) ⁷⁴	likelihood for	higher spirochete loads
		disseminated	compared to female mice ⁷⁹
	Females >45 have	disease ⁷⁷	
	greater incidence		
Borrelia burgdorferi	(Sweden 1992-1993) ^{75,76}	Lyme neuroborreliosis	
(Lyme disease)		is more common in	
	Females are more likely	female patients ⁷⁸	
	to be re-infected after 5		
	years. ^{75,76}	Females have	
		increased production	
		of IFNγ, IL-4, IL6, IL-	
		10, TNF ⁷⁵	
	Malaa haya hishar	Malaa aybibit birbar	Male mice have accelerated
	Males have higher	Males exhibit higher mortality rates	
	incidence (male/female		disease progression, increased
	ratio is 1.7) ⁸⁰	(global) ⁸¹	morbidity and mortality ⁸³
Mycobacterium		Pregnancy increases	Males have higher <i>M.</i>
tuberculosis		risk of disease	tuberculosis loads ⁸³
		complications ⁸²	
		oompricatione	Testosterone treatment
		Females usually have	increases susceptibility to
		less symptoms ⁶⁹	infection ⁸³
			Male mice are more susceptibl
			than female mice, and they
Mycoplasma			develop more severe disease i
pulmonis			lung parenchyma. Removal of
			reproductive organs in males
			reduced disease severity ⁸⁴
	Males have higher	Males are more likely	Male mice have higher bacteria
	incidence ⁸⁵	to become	loads ⁶⁹
		sympotomatic with Q	
		fever (symptoms	Estrogen treatment of
		include fever,	ovariectomized mice reduces
		granulomatous	bacterial loads and granulomas
		hepatitis, myocarditis,	
Coxiella burnettii		pericarditis,	C. burnetti infection results in
		pneumonia) ^{69,85}	sex-specific gene expression
		Brognanov increases	profiles: males upregulate IL-1
		Pregnancy increases	and IFNγ production; females
		risk for persistent infections, and	exhibit altered expression of
		impaired immunity	circadian rhythm genes.87
		negatively impacts	
		pregnancy ⁶⁹	
		pregnancy	

Campylobacter	Males have higher incidence69		Male mice are more susceptible to infection and colonization ⁸⁸
spp.			Males have higher shedding rates ⁸⁸
Clostridiodes difficile	Females have higher incidence ⁸⁹ Females have increased risk of recurrent infection ⁶¹	Increased disease severity in pregnant and peripartum females ⁸⁹	Progesterone and estrogen intermediates can inhibit spore germination in mice ⁶¹
Listeria monocytogenes	Females have higher incidence rates of invasive listeriosis ⁹⁰ Pregnant females have higher incidence ⁶⁹ Among older individuals, males have 2-4 higher incidence rates ⁹⁰	Pregnant females and older males have greater incidences of invasive disease ⁹⁰ Older males have increased fatality rates ⁹⁰	Female mice are more susceptible to infection and exhibit greater lethality ⁹¹ Female mice have higher bacterial load; Infected females have increased IL-10, which inhibits Th1 differentiation and Th1-derived cytokines ⁹¹ Estrogen treatment reduced IL- 12, IFNγ and TNF, increased IL- 4 and IL-10, and reduced monocytes and lymphocyte accumulation at infection ⁹²
Legionella pneumophila	Males have higher incidence, with male:female ratios of 1.7 to 5 in U.S, Europe, Australia, Japan ⁶⁹	Males are more likely to develop legionellosis and to have a poor prognosis ⁶⁹	n/a
Leptospira spp.	Males have higher incidence ⁶⁹		n/a
Francisella tularensis	Males have higher incidence ⁶⁵		No sex difference with regards to susceptibility. However, vaccinated female mice are more resistant to infection, with lower bacterial burdens, less tissue inflammation, and less proinflammatory cytokine production, and have more <i>F.</i> <i>tularensis</i> -specific antibodies in serum and lung ⁸⁵
Escherichia coli	Females have higher incidence ⁶⁹		No sex difference with enterohemorrhagic <i>E.coli</i> disease in mice ⁶⁹
Treponema pallidum (syphilis)	Males have higher incidence ^{93,94}		n/a
Neisseria gonorrhea	Males have higher incidence ⁶⁹ Infected males may also have increased expression of gonococcal	Most females lack symptoms ⁶⁹ Complications in males include epididymitis, infertility,	Estrogen treated mice have increased susceptibility to gonococcal infection ⁹⁸

				1
		antimicrobial resistance genes ⁹⁵	prostatitis, seminal vesiculitis ⁹⁶	
		yoneo	veoleuliuo	
			Elevated progesterone	
			promotes gonococcal	
			infection (human	
			cervical epithelial	
			cells) ⁹⁷	
		Males have higher	Males have greater	Male mice are more susceptible
		incidence for all types of	hospitalization rates	& have more severe disease ¹⁰⁰
		pneumonia ⁶⁹	and increased	
			mortality ⁶⁹	Males exhibit increased levels of
	Streptococcus	Males (pre-puberty) have	Malaa ara mara	pro-inflammatory cytokines (IL-6,
	pneumoniae	higher incidence	Males are more frequently diagnosed	IL-17A, IFNγ) ¹⁰⁰
			with Legionellosis	Estrogen is protective and
			(1.7:5 male to female	regulates macrophage activity
			ratio) ⁹⁹	(for pneumococcal
				pneumonia) ¹⁰¹
		Males have higher	Males have higher	n/a
		incidence for	levels of IgG4	
		Yersiniosis ¹⁰²	antibodies for Yersinia	
	Yersinia		outer membrane	
	enterocolitica		proteins, which is	
			associated with an	
			anti-inflammatory response that is	
			resistant to treatment ⁶¹	
		Males have higher rates	Conflicting results	Male mice develop greater
		of sepsis and septic	regarding a sex bias	inflammatory responses,
		shock ⁶⁵	for mortality ¹⁰³	producing more pro-
				inflammatory cytokines ⁶⁹
		Males are more likely to		
	Sepsis:	develop sepsis after		Males have more severe sepsis-
	Staphylococcus, Escherichia coli,	trauma or surgery ⁶⁵		induced cardiac dysfunction ⁸⁵
	Pseduomonas, etc			Estragon is protective, and
	rseuuomonas, elc			Estrogen is protective, and female mice produced protective
				antibodies in response to
				estrogen; estrogen-driven
				antibodies were maternally
				transferrable to offspring ¹⁰⁴
		Females have higher	Female patients have	Estrogen increases and
		incidence in some	greater number of	androgens decreases parasite
		countries (Nigeria,	transitional cysts ¹⁰⁶	loads in mice, either acting
		Tanzania, Guatemala) ¹⁰⁵		directly on the worm's
١S	Pork tapeworm	Females have more		reproduction or by altering host's immune response to favor T⊦2 or
R	(Taenia solium)	transitional cysts in brain		$T_{\rm H}$ 1 pathways, respectively
WORMS	Neurocysticercosis	(Ecuador) ¹⁰⁶		(Taenia crassiceps) ¹⁰⁷
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		No sex difference with		
		regards to incidence in		
		Vietnam ¹⁰⁵		

	A 1	Females have higher		n/a
	A. Lumbricoides	incidence ¹⁰⁸		
		Males have higher prevalence of infection ¹⁰⁹		Female and castrated male mice have greater morbidity after Schistosoma infection ¹¹⁰
				Female mice have higher worm loads ¹¹⁰
	Schistosoma masoni			Testosterone is protective for Schistosoma mansoni infections; female mice treated with testosterone had reduced worm burdens (if treated before infection) ¹¹⁰
	Plasmodium falciparum (malaria)		Male patients have greater disease severity ¹¹¹	n/a
	Cryptosporidium	Males have higher incidence ¹¹²	Male patients have greater incidence of hospitalizations ¹¹³	n/a
	Entamoeba histolytica (amoebiasis)	Asymtopmatic infection rates are the same across sexes ¹¹⁴	Invasive amebiasis predominantly affects males; males have higher rates of invasive disease ¹¹⁴	Testosterone treatment induces proinflammatory responses in mouse (& human) classical monocytes, with increased production of CXCL1 and TNF ¹¹⁵
S			Males have higher incidence of hepatic amebiasis ¹¹⁵	
ASITES		Males have higher incidence even when accounting for exposure ¹¹⁶	Male patients exhibit higher rates of treatment failure and adverse effects ¹¹⁶	Male mice have higher parasite burdens following infection (L.infantum) ¹²¹
PAR		Adult males have higher incidence of cutaneous leishmaniasis ¹¹⁷		Male mice express higher levels of IL-10 and TNF after infection and exhibit greater disease severity ¹²¹
	Leishmania	Childhood cutaneous leishmaniasis does not exhibit a sex bias ¹¹⁸		Male mice (BALB/c congenic strains) are more susceptible to subcutanteous L.major, and exhibit more severe
		Males have higher incidence and greater risk ratio of visceral		disease ^{116,122} Female mice heal small lesions
		leishmaniasis ¹¹⁹ No sex bias for childhood cutaneous leishmaniasis ¹²⁰		following L. Mexicana infection, yet male mice exhibit persistent lesions, dependent on IL-4 levels ¹²³

			Sex differences with	Male hamsters have increased disease severity and parasite burden with L. viannia infection. Testosterone-treated female animals had larger lesions than untreated females. Disease severity correlated with increased expression of IL-4, IL- 10, and TGF β^{124} X-linked <i>Cxcr3</i> is biallelically expressed in T cells of female mice and contributes to increased cytokine production ¹²⁵ Female mice are more
			regards to infection- induced behavioral changes and personality shifts ¹²⁶	Susceptible to infection and have higher cyst burdens ¹²⁷ Female mice exhibit higher mortality after acute infection ¹²⁷
	Toxoplasma gondii			Male mice produce higher levels of TNF after day 10 of infection; mortality of female mice did not correlate with lower TNF levels. Male mice produce higher levels of IFN γ and IL-10 early during infection ¹²⁷
	Aspergillus fumigatus	Males have higher incidence (invasive pulmonary aspergillosis) ¹²⁸ Male bias with regards to prevalence, incidence and severity ¹²⁹ Males more susceptible to infection ¹²⁹		Female mice have higher antibody titers and levels of neutrophils, eosinophils and lymphocytes after infection ¹³⁰
FUNGI	Cryptococcus neoformans	Males have higher incidence, with 3:1 male to female rations for HIV negative populations and 8:2 among HIV positive populations ¹³¹	Males with cryptococcosis have more severe symptoms and worse outcomes ¹³¹	Female mice express more cytokines in the plasma and have increased expression of TNF and IFN γ in spleen ¹³² Increased lethality for young male mice ¹³² Survival and fungal loads are similar between male and female mice ¹³²
	Paracoccidioides brasiliensis	Males have greater incidence (10:1 male to female ratio in Latin America) ¹³³	Male patients have faster disease progression ¹³⁴	Male mice are more susceptible ¹³⁵

				Macrophages from infected female mice exhibit greater fungicidal activity, with higher nitric oxide production ¹³⁵ Estrogen is protective following P. brasiliensis infection, as castrated male treated with estradiol have higher levels of IFN γ and lower levels of IL-10 compared to normal males. Ovariectomized female mice treated with testosterone produce less IFN γ and more IL- 10 compared to normal female mice after infection ¹³⁵
	<i>Microsporum,</i> <i>Trichophyton,</i> <i>epigermophyton</i> (Tinea or Dermatophytosi)	Males have higher incidence ¹³⁶		n/a
	Candida albicans	Females have higher incidence (oral candidiasis) ¹³⁷ Females have higher incidence (candida onychomycosis), with 3/4 females (childbearing age) infected at least once in their life; and 1/10 females having a recurring event ¹³⁷	Male patients with seropositivity for <i>C.albicans</i> have increased odds for schizopherenia ¹³⁸ Female patients with seropositivity for <i>C.albicans</i> have increased odds for lower cognitive scores ¹³⁸	n/a

- 1 Alwani, M. *et al.* Sex-based differences in severity and mortality in COVID-19. *Reviews in Medical Virology* **31** (2021). <u>https://doi.org:10.1002/rmv.2223</u>
- 2 Haitao, T. *et al.* COVID-19 and Sex Differences. *Mayo Clinic Proceedings* **95**, 2189-2203 (2020). <u>https://doi.org:10.1016/j.mayocp.2020.07.024</u>
- 3 Jin, S. *et al.* Sex- and age-specific clinical and immunological features of coronavirus disease 2019. *PLOS Pathogens* **17**, e1009420 (2021). https://doi.org:10.1371/journal.ppat.1009420
- 4 Gemmati, D. *et al.* COVID-19 and Individual Genetic Susceptibility/Receptivity: Role of ACE1/ACE2 Genes, Immunity, Inflammation and Coagulation. Might the Double X-Chromosome in Females Be Protective against SARS-CoV-2 Compared to the Single X-Chromosome in Males? *International Journal of Molecular Sciences* **21**, 3474 (2020). https://doi.org:10.3390/ijms21103474
- 5 Gebhard, C., Regitz-Zagrosek, V., Neuhauser, H. K., Morgan, R. & Klein, S. L. Impact of sex and gender on COVID-19 outcomes in Europe. *Biology of Sex Differences* **11**, 29 (2020). <u>https://doi.org:10.1186/s13293-020-00304-9</u>
- 6 Scully, E. P., Haverfield, J., Ursin, R. L., Tannenbaum, C. & Klein, S. L. Considering how biological sex impacts immune responses and COVID-19 outcomes. *Nature Reviews Immunology* **20**, 442-447 (2020). <u>https://doi.org:10.1038/s41577-020-0348-8</u>

- 7 Takahashi, T. *et al.* Sex differences in immune responses to SARS-CoV-2 that underlie disease outcomes. *medRxiv*, 2020.2006.2006.20123414 (2020). https://doi.org:10.1101/2020.06.06.20123414
- 8 Silva, M. V. R. *et al.* Men are the main COVID-19 transmitters: behavior or biology? *Discover Mental Health* **2** (2022). <u>https://doi.org:10.1007/s44192-022-00004-3</u>
- 9 O'Driscoll, M. *et al.* Age-specific mortality and immunity patterns of SARS-CoV-2. *Nature* **590**, 140-145 (2021). <u>https://doi.org:10.1038/s41586-020-2918-0</u>
- 10 Harwood, R. *et al.* Which children and young people are at higher risk of severe disease and death after hospitalisation with SARS-CoV-2 infection in children and young people: A systematic review and individual patient meta-analysis. *eClinicalMedicine* **44**, 101287 (2022). <u>https://doi.org:10.1016/j.eclinm.2022.101287</u>
- 11 Sylvester, S. V. *et al.* Sex differences in sequelae from COVID-19 infection and in long COVID syndrome: a review. *Current Medical Research and Opinion*, 1-9 (2022). https://doi.org:10.1080/03007995.2022.2081454
- 12 Taquet, M. *et al.* Incidence, co-occurrence, and evolution of long-COVID features: A 6month retrospective cohort study of 273,618 survivors of COVID-19. *PLoS Med* **18**, e1003773 (2021). <u>https://doi.org:10.1371/journal.pmed.1003773</u>
- 13 Channappanavar, R. *et al.* Sex-Based Differences in Susceptibility to Severe Acute Respiratory Syndrome Coronavirus Infection. *The Journal of Immunology* **198**, 4046 (2017). <u>https://doi.org:10.4049/jimmunol.1601896</u>
- 14 Sohn, S.-Y. *et al.* Interferon-Lambda Intranasal Protection and Differential Sex Pathology in a Murine Model of SARS-CoV-2 Infection. *mBio* **12** (2021). https://doi.org:10.1128/mbio.02756-21
- 15 Francis, M. E. *et al.* Sex and age bias viral burden and interferon responses during SARS-CoV-2 infection in ferrets. *Scientific Reports* **11** (2021). https://doi.org:10.1038/s41598-021-93855-9
- 16 Stelzig, K. E. *et al.* Estrogen regulates the expression of SARS-CoV-2 receptor ACE2 in differentiated airway epithelial cells. *American Journal of Physiology-Lung Cellular and Molecular Physiology* **318**, L1280-L1281 (2020). https://doi.org:10.1152/ajplung.00153.2020
- 17 Devaux, C. A., Rolain, J.-M. & Raoult, D. ACE2 receptor polymorphism: Susceptibility to SARS-CoV-2, hypertension, multi-organ failure, and COVID-19 disease outcome. *Journal of microbiology, immunology and infection = Wei mian yu gan ran za zhi.* **53**, 425-435 (2020). <u>https://doi.org:10.1016/j.jmii.2020.04.015</u>
- 18 Klein SL, Pekosz A, Passaretti C, Anker M & Olukoya P. (World Health Organization, 2010).
- 19 Noymer, A. & Garenne, M. The 1918 influenza epidemic's effects on sex differentials in mortality in the United States. *Popul Dev Rev* **26**, 565-581 (2000). https://doi.org:10.1111/j.1728-4457.2000.00565.x
- 20 Eshima, N. *et al.* Sex- and age-related differences in morbidity rates of 2009 pandemic influenza A H1N1 virus of swine origin in Japan. *PLoS One* **6**, e19409 (2011). https://doi.org:10.1371/journal.pone.0019409
- 21 Jacobs, J. H. *et al.* Searching for sharp drops in the incidence of pandemic A/H1N1 influenza by single year of age. *PLoS One* **7**, e42328 (2012). https://doi.org:10.1371/journal.pone.0042328
- 22 Jensen-Fangel, S. *et al.* Gender differences in hospitalization rates for respiratory tract infections in Danish youth. *Scand J Infect Dis* **36**, 31-36 (2004). <u>https://doi.org:10.1080/00365540310017618</u>
- 23 Vom Steeg, L. G. & Klein, S. L. Sex and sex steroids impact influenza pathogenesis across the life course. *Semin Immunopathol* **41**, 189-194 (2019). https://doi.org:10.1007/s00281-018-0718-5

- 24 Giurgea, L. T. *et al.* Sex Differences in Influenza: The Challenge Study Experience. *J* Infect Dis **225**, 715-722 (2022). <u>https://doi.org:10.1093/infdis/jiab422</u>
- 25 Klein, S. L., Hodgson, A. & Robinson, D. P. Mechanisms of sex disparities in influenza pathogenesis. *J Leukoc Biol* **92**, 67-73 (2012). <u>https://doi.org:10.1189/jlb.0811427</u>
- 26 Cervantes, O. *et al.* Role of hormones in the pregnancy and sex-specific outcomes to infections with respiratory viruses*. *Immunological Reviews* **308**, 123-148 (2022). https://doi.org:10.1111/imr.13078
- 27 Herold, S., Becker, C., Ridge, K. M. & Budinger, G. R. Influenza virus-induced lung injury: pathogenesis and implications for treatment. *Eur Respir J* **45**, 1463-1478 (2015). https://doi.org:10.1183/09031936.00186214
- 28 Kumar, A. *et al.* Critically ill patients with 2009 influenza A(H1N1) infection in Canada. *JAMA* **302**, 1872-1879 (2009). <u>https://doi.org:10.1001/jama.2009.1496</u>
- 29 Lorenzo, M. E. *et al.* Antibody responses and cross protection against lethal influenza A viruses differ between the sexes in C57BL/6 mice. *Vaccine* **29**, 9246-9255 (2011). https://doi.org:10.1016/j.vaccine.2011.09.110
- 30 Fink, A. L., Engle, K., Ursin, R. L., Tang, W.-Y. & Klein, S. L. Biological sex affects vaccine efficacy and protection against influenza in mice. *Proceedings of the National Academy of Sciences* **115**, 12477 (2018). <u>https://doi.org:10.1073/pnas.1805268115</u>
- 31 Lorenzo, M. E. *et al.* Antibody responses and cross protection against lethal influenza A viruses differ between the sexes in C57BL/6 mice. *Vaccine.* **29**, 9246-9255 (2011). <u>https://doi.org:10.1016/j.vaccine.2011.09.110</u>
- 32 Vermillion, M. S. *et al.* Production of amphiregulin and recovery from influenza is greater in males than females. *Biol Sex Differ* **9**, 24 (2018). <u>https://doi.org:10.1186/s13293-018-0184-8</u>
- 33 vom Steeg, L. G., Attreed, S. E., Zirkin, B. & Klein, S. L. Testosterone treatment of aged male mice improves some but not all aspects of age-associated increases in influenza severity. *Cellular Immunology* **345**, 103988 (2019). https://doi.org/https://doi.org/10.1016/j.cellimm.2019.103988
- 34 Vom Steeg, L. G. *et al.* Androgen receptor signaling in the lungs mitigates inflammation and improves the outcome of influenza in mice. *PLoS Pathog* **16**, e1008506 (2020). <u>https://doi.org:10.1371/journal.ppat.1008506</u>
- 35 Vom Steeg, L. G. *et al.* Age and testosterone mediate influenza pathogenesis in male mice. *Am J Physiol Lung Cell Mol Physiol* **311**, L1234-L1244 (2016). <u>https://doi.org:10.1152/ajplung.00352.2016</u>
- 36 Vermillion, M. S., Ursin, R. L., Attreed, S. E. & Klein, S. L. Estriol Reduces Pulmonary Immune Cell Recruitment and Inflammation to Protect Female Mice From Severe Influenza. *Endocrinology* **159**, 3306-3320 (2018). https://doi.org:10.1210/en.2018-00486
- 37 Chen, C. M., Chen, S. C. C., Yang, H. Y., Yang, S. T. & Wang, C. M. Hospitalization and mortality due to hepatitis A in Taiwan: a 15-year nationwide cohort study. *Journal of Viral Hepatitis* **23**, 940-945 (2016). https://doi.org:10.1111/jvh.12564
- 38 Baden, R., Rockstroh, J. K. & Buti, M. Natural history and management of hepatitis C: does sex play a role? *J Infect Dis* **209 Suppl 3**, S81-85 (2014). <u>https://doi.org:10.1093/infdis/jiu057</u>
- 39 Jean, C. M., Honarmand, S., Louie, J. K. & Glaser, C. A. Risk factors for West Nile virus neuroinvasive disease, California, 2005. *Emerg Infect Dis* **13**, 1918-1920 (2007). https://doi.org:10.3201/eid1312.061265
- 40 Hoffman, K. W. *et al.* Sex differences in cytokine production following West Nile virus infection: Implications for symptom manifestation. *Pathog Dis* **77** (2019). https://doi.org:10.1093/femspd/ftz016

- 41 Hegdahl, H. K., Fylkesnes, K. M., Sandøy, I. F. & Faragher, E. B. Sex Differences in HIV Prevalence Persist over Time: Evidence from 18 Countries in Sub-Saharan Africa. *PloS* one. **11**, e0148502 (2016). <u>https://doi.org:10.1371/journal.pone.0148502</u>
- 42 Griesbeck, M., Scully, E. & Altfeld, M. Sex and gender differences in HIV-1 infection. *Clinical science.* **130**, 1435-1451 (2016). <u>https://doi.org:10.1042/cs20160112</u>
- 43 Meier, A. *et al.* Sex differences in the Toll-like receptor-mediated response of plasmacytoid dendritic cells to HIV-1. *Nat Med* **15**, 955-959 (2009). <u>https://doi.org:10.1038/nm.2004</u>
- 44 Nicolosi, A. *et al.* The Efficiency of Male-to Female and Female-to-Male Sexual Transmission of the Human Immunodeficiency Virus. *Epidemiology*. **5**, 570-575 (1994). https://doi.org:10.1097/00001648-199411000-00003
- 45 Cobelens, F., Nagelkerke, N. & Fletcher, H. The convergent epidemiology of tuberculosis and human cytomegalovirus infection. *F1000Research* **7**, 280 (2018). https://doi.org:10.12688/f1000research.14184.2
- 46 Cox, M. *et al.* Sex-Differential Impact of Human Cytomegalovirus Infection on In Vitro Reactivity to Toll-Like Receptor 2, 4 and 7/8 Stimulation in Gambian Infants. *Vaccines (Basel)* **8** (2020). <u>https://doi.org:10.3390/vaccines8030407</u>
- 47 Yousuf, W., Ibrahim, H., Harfouche, M., Abu Hijleh, F. & Abu-Raddad, L. Herpes simplex virus type 1 in Europe: systematic review, meta-analyses and meta-regressions. *BMJ global health.* **5**, e002388 (2020). <u>https://doi.org:10.1136/bmjgh-2020-002388</u>
- 48 McQuillan, G., Kruszon-Moran, D., Flagg, E. W. & Paulose-Ram, R. Prevalence of Herpes Simplex Virus Type 1 and Type 2 in Persons Aged 14-49: United States, 2015-2016. *NCHS Data Brief*, 1-8 (2018).
- 49 Geurs, T. L., Hill, E. B., Lippold, D. M. & French, A. R. Sex differences in murine susceptibility to systemic viral infections. *J Autoimmun* **38**, J245-253 (2012). https://doi.org:10.1016/j.jaut.2011.12.003
- 50 Han, X. *et al.* Gender influences herpes simplex virus type 1 infection in normal and gamma interferon-mutant mice. *J Virol* **75**, 3048-3052 (2001). https://doi.org:10.1128/JVI.75.6.3048-3052.2001
- 51 Huber, S. A. & Pfaeffle, B. Differential Th1 and Th2 cell responses in male and female BALB/c mice infected with coxsackievirus group B type 3. *J Virol* **68**, 5126-5132 (1994). https://doi.org:10.1128/JVI.68.8.5126-5132.1994
- 52 WHO Ebola Response Team, J. A.-A., , Archchun Ariyarajah, Isobel M. Blake, Anne Cori, Christl A. Donnelly, Ilaria Dorigatti, Christopher Dye, Tim Eckmanns, Neil M. Ferguson, Christophe Fraser, Tini Garske, Wes Hinsley, Thibaut Jombart, Harriet L. Mills, Gemma Nedjati-Gilani, Emily Newton, Pierre Nouvellet, Devin Perkins, Steven Riley, Dirk Schumacher, Anita Shah, Lisa J. Thomas, Maria D. Van Kerkhove. Ebola Virus Disease among Male and Female Persons in West Africa. *New England Journal of Medicine* **374**, 96-98 (2016). <u>https://doi.org:10.1056/nejmc1510305</u>
- 53 Garenne, M. Sex Differences in Measles Mortality: A World Review. *International journal of epidemiology.* **23**, 632-642 (1994). <u>https://doi.org:10.1093/ije/23.3.632</u>
- 54 Green, M. S., Schwartz, N. & Peer, V. Gender differences in measles incidence rates in a multi-year, pooled analysis, based on national data from seven high income countries. BMC Infectious Diseases **22** (2022). <u>https://doi.org:10.1186/s12879-022-07340-3</u>
- 55 Schuurhof, A. *et al.* Interleukin-9 polymorphism in infants with respiratory syncytial virus infection: An opposite effect in boys and girls. *Pediatric pulmonology.* **45**, 608-613 (2010). <u>https://doi.org:10.1002/ppul.21229</u>
- 56 Pisesky, A. *et al.* Incidence of Hospitalization for Respiratory Syncytial Virus Infection amongst Children in Ontario, Canada: A Population-Based Study Using Validated Health Administrative Data. *PLOS ONE* **11**, e0150416 (2016). https://doi.org:10.1371/journal.pone.0150416

- 57 Kenmoe, S. *et al.* Prevalence of human respiratory syncytial virus infection in people with acute respiratory tract infections in Africa: A systematic review and meta-analysis. *Influenza and Other Respiratory Viruses* **12**, 793-803 (2018). <u>https://doi.org:10.1111/irv.12584</u>
- 58 Malinczak, C. A. *et al.* Sex-associated TSLP-induced immune alterations following earlylife RSV infection leads to enhanced allergic disease. *Mucosal Immunol* **12**, 969-979 (2019). <u>https://doi.org:10.1038/s41385-019-0171-3</u>
- 59 Ferro, A. *et al.* Sex differences in the prevalence of Helicobacter pylori infection: an individual participant data pooled analysis (StoP Project). *Eur J Gastroenterol Hepatol* **31**, 593-598 (2019). <u>https://doi.org:10.1097/MEG.00000000001389</u>
- 60 Murray, L. J., McCrum, E. E., Evans, A. E. & Bamford, K. B. Epidemiology of Helicobacter pylori infection among 4742 randomly selected subjects from Northern Ireland. *Int J Epidemiol* **26**, 880-887 (1997). <u>https://doi.org:10.1093/ije/26.4.880</u>
- 61 Vazquez-Martinez, E. R., Garcia-Gomez, E., Camacho-Arroyo, I. & Gonzalez-Pedrajo, B. Sexual dimorphism in bacterial infections. *Biol Sex Differ* **9**, 27 (2018). <u>https://doi.org:10.1186/s13293-018-0187-5</u>
- 62 Ohtani, M. *et al.* 17 beta-estradiol suppresses Helicobacter pylori-induced gastric pathology in male hypergastrinemic INS-GAS mice. *Carcinogenesis* **32**, 1244-1250 (2011). <u>https://doi.org:10.1093/carcin/bgr072</u>
- 63 Harness-Brumley, C. L., Elliott, A. C., Rosenbluth, D. B., Raghavan, D. & Jain, R. Gender differences in outcomes of patients with cystic fibrosis. *J Womens Health* (*Larchmt*) **23**, 1012-1020 (2014). <u>https://doi.org:10.1089/jwh.2014.4985</u>
- 64 FitzSimmons, S. C. The changing epidemiology of cystic fibrosis. *J Pediatr* **122**, 1-9 (1993). <u>https://doi.org:10.1016/s0022-3476(05)83478-x</u>
- 65 Guilbault, C. *et al.* Influence of gender and interleukin-10 deficiency on the inflammatory response during lung infection with Pseudomonas aeruginosa in mice. *Immunology* **107**, 297-305 (2002). <u>https://doi.org:10.1046/j.1365-2567.2002.01508.x</u>
- 66 Peer, V., Schwartz, N. & Green, M. S. Sex Differences in Salmonellosis Incidence Rates-An Eight-Country National Data-Pooled Analysis. *J Clin Med* **10** (2021). https://doi.org:10.3390/jcm10245767
- 67 Blasi, F., Tarsia, P., Arosio, C., Fagetti, L. & Allegra, L. Epidemiology of Chlamydia pneumoniae. *Clin Microbiol Infect* **4 Suppl 4**, S1-S6 (1998).
- 68 Matteelli, A. *et al.* Prevalence of Chlamydia trachomatis and Neisseria gonorrhoeae infection in adolescents in Northern Italy: an observational school-based study. *BMC Public Health* **16**, 200 (2016). <u>https://doi.org:10.1186/s12889-016-2839-x</u>
- 69 Dias, S. P., Brouwer, M. C. & van de Beek, D. Sex and Gender Differences in Bacterial Infections. *Infect Immun* **90**, e0028322 (2022). <u>https://doi.org:10.1128/iai.00283-22</u>
- 70 Dielissen, P. W., Teunissen, D. A. & Lagro-Janssen, A. L. Chlamydia prevalence in the general population: is there a sex difference? a systematic review. *BMC Infect Dis* 13, 534 (2013). <u>https://doi.org:10.1186/1471-2334-13-534</u>
- 71 Hannu, T. Reactive arthritis. *Best Pract Res Clin Rheumatol* **25**, 347-357 (2011). <u>https://doi.org:10.1016/j.berh.2011.01.018</u>
- 72 Zheng, R. *et al.* A Systematic Review and Meta-Analysis of Epidemiology and Clinical Manifestations of Human Brucellosis in China. *Biomed Res Int* **2018**, 5712920 (2018). https://doi.org:10.1155/2018/5712920
- 73 Alkahtani, A. M., Assiry, M. M., Chandramoorthy, H. C., Al-Hakami, A. M. & Hamid, M. E. Sero-prevalence and risk factors of brucellosis among suspected febrile patients attending a referral hospital in southern Saudi Arabia (2014-2018). *BMC Infect Dis* 20, 26 (2020). <u>https://doi.org:10.1186/s12879-020-4763-z</u>
- 74 Orloski, K. A., Hayes, E. B., Campbell, G. L. & Dennis, D. T. Surveillance for Lyme disease--United States, 1992-1998. *MMWR CDC Surveill Summ* **49**, 1-11 (2000).

- 75 Jarefors, S. *et al.* Lyme borreliosis reinfection: might it be explained by a gender difference in immune response? *Immunology* **118**, 224-232 (2006). <u>https://doi.org:10.1111/j.1365-2567.2006.02360.x</u>
- 76 Berglund, J. *et al.* An epidemiologic study of Lyme disease in southern Sweden. *N Engl J Med* **333**, 1319-1327 (1995). <u>https://doi.org:10.1056/NEJM199511163332004</u>
- 77 Schwartz, A. M. *et al.* Epidemiology and cost of Lyme disease-related hospitalizations among patients with employer-sponsored health insurance-United States, 2005-2014. *Zoonoses Public Health* **67**, 407-415 (2020). <u>https://doi.org:10.1111/zph.12699</u>
- 78 Kwit, N. A., Nelson, C. A., Max, R. & Mead, P. S. Risk Factors for Clinician-Diagnosed Lyme Arthritis, Facial Palsy, Carditis, and Meningitis in Patients From High-Incidence States. *Open Forum Infect Dis* **5**, ofx254 (2018). <u>https://doi.org:10.1093/ofid/ofx254</u>
- 79 Zinck, C. B. *et al.* Borrelia burgdorferi strain and host sex influence pathogen prevalence and abundance in the tissues of a laboratory rodent host. *Mol Ecol* **31**, 5872-5888 (2022). <u>https://doi.org:10.1111/mec.16694</u>
- 80 Hertz, D. & Schneider, B. Sex differences in tuberculosis. *Semin Immunopathol* **41**, 225-237 (2019). <u>https://doi.org:10.1007/s00281-018-0725-6</u>
- 81 Tan, W. *et al.* Sex influences the association between haemostasis and the extent of lung lesions in tuberculosis. *Biol Sex Differ* **9**, 44 (2018). <u>https://doi.org:10.1186/s13293-018-0203-9</u>
- Miele, K., Bamrah Morris, S. & Tepper, N. K. Tuberculosis in Pregnancy. Obstet Gynecol 135, 1444-1453 (2020). <u>https://doi.org:10.1097/AOG.00000000003890</u>
- Bibbern, J., Eggers, L. & Schneider, B. E. Sex differences in the C57BL/6 model of Mycobacterium tuberculosis infection. *Sci Rep* 7, 10957 (2017). https://doi.org:10.1038/s41598-017-11438-z
- Yancey, A. L., Watson, H. L., Cartner, S. C. & Simecka, J. W. Gender is a major factor in determining the severity of mycoplasma respiratory disease in mice. *Infect Immun* 69, 2865-2871 (2001). https://doi.org/10.1128/IAI.69.5.2865-2871.2001
- 85 Raoult, D., Marrie, T. & Mege, J. Natural history and pathophysiology of Q fever. *Lancet Infect Dis* **5**, 219-226 (2005). <u>https://doi.org:10.1016/S1473-3099(05)70052-9</u>
- 86 Leone, M. *et al.* Effect of sex on Coxiella burnetii infection: protective role of 17betaestradiol. *J Infect Dis* **189**, 339-345 (2004). <u>https://doi.org:10.1086/380798</u>
- 87 Textoris, J. *et al.* Sex-related differences in gene expression following Coxiella burnetii infection in mice: potential role of circadian rhythm. *PLoS One* **5**, e12190 (2010). https://doi.org:10.1371/journal.pone.0012190
- 88 Strachan, N. J. *et al.* Sexual dimorphism in campylobacteriosis. *Epidemiol Infect* **136**, 1492-1495 (2008). <u>https://doi.org:10.1017/S0950268807009934</u>
- 89 Turner, N. A. *et al.* Epidemiologic Trends in Clostridioides difficile Infections in a Regional Community Hospital Network. *JAMA Netw Open* **2**, e1914149 (2019). <u>https://doi.org:10.1001/jamanetworkopen.2019.14149</u>
- 90 Pohl, A. M. *et al.* Differences Among Incidence Rates of Invasive Listeriosis in the U.S. FoodNet Population by Age, Sex, Race/Ethnicity, and Pregnancy Status, 2008-2016. *Foodborne Pathog Dis* **16**, 290-297 (2019). <u>https://doi.org:10.1089/fpd.2018.2548</u>
- 91 Pasche, B. *et al.* Sex-dependent susceptibility to Listeria monocytogenes infection is mediated by differential interleukin-10 production. *Infect Immun* **73**, 5952-5960 (2005). https://doi.org:10.1128/IAI.73.9.5952-5960.2005
- 92 Salem, M. L., Matsuzaki, G., Madkour, G. A. & Nomoto, K. Beta-estradiol-induced decrease in IL-12 and TNF-alpha expression suppresses macrophage functions in the course of Listeria monocytogenes infection in mice. *Int J Immunopharmacol* 21, 481-497 (1999). <u>https://doi.org:10.1016/s0192-0561(99)00027-2</u>

- 93 Bremer, V., Marcus, U. & Hamouda, O. Syphilis on the rise again in Germany results from surveillance data for 2011. *Eurosurveillance* **17** (2012). <u>https://doi.org:10.2807/ese.17.29.20222-en</u>
- 94 Peeling, R. W. *et al.* Syphilis. *Nature Reviews Disease Primers* **3** (2017). <u>https://doi.org:10.1038/nrdp.2017.73</u>
- 95 Nudel, K. *et al.* Transcriptome Analysis of Neisseria gonorrhoeae during Natural Infection Reveals Differential Expression of Antibiotic Resistance Determinants between Men and Women. *mSphere* **3** (2018). <u>https://doi.org:10.1128/mSphereDirect.00312-18</u>
- 96 Xiong, M. *et al.* Analysis of the sex ratio of reported gonorrhoea incidence in Shenzhen, China. *BMJ Open* **6**, e009629 (2016). <u>https://doi.org:10.1136/bmjopen-2015-009629</u>
- 97 Wu, Z. *et al.* The relationship between the symptoms of female gonococcal infections and serum progesterone level and the genotypes of Neisseria gonorrhoeae multi-antigen sequence type (NG-MAST) in Wuhan, China. *Eur J Clin Microbiol Infect Dis* **30**, 113-116 (2011). <u>https://doi.org:10.1007/s10096-010-1040-x</u>
- 98 Jerse, A. E. *et al.* Estradiol-Treated Female Mice as Surrogate Hosts for Neisseria gonorrhoeae Genital Tract Infections. *Front Microbiol* **2**, 107 (2011). https://doi.org:10.3389/fmicb.2011.00107
- 99 Farnham, A., Alleyne, L., Cimini, D. & Balter, S. Legionnaires' disease incidence and risk factors, New York, New York, USA, 2002-2011. *Emerg Infect Dis* **20**, 1795-1802 (2014). https://doi.org:10.3201/eid2011.131872
- 100 Kadioglu, A. *et al.* Sex-based differences in susceptibility to respiratory and systemic pneumococcal disease in mice. *J Infect Dis* **204**, 1971-1979 (2011). https://doi.org:10.1093/infdis/jir657
- 101 Yang, Z. *et al.* Female resistance to pneumonia identifies lung macrophage nitric oxide synthase-3 as a therapeutic target. *Elife* **3** (2014). <u>https://doi.org:10.7554/eLife.03711</u>
- 102 Rosner, B. M., Stark, K. & Werber, D. Epidemiology of reported Yersinia enterocolitica infections in Germany, 2001-2008. *BMC Public Health* **10**, 337 (2010). https://doi.org:10.1186/1471-2458-10-337
- 103 Pietropaoli, A. P., Glance, L. G., Oakes, D. & Fisher, S. G. Gender differences in mortality in patients with severe sepsis or septic shock. *Gend Med* **7**, 422-437 (2010). https://doi.org:10.1016/j.genm.2010.09.005
- 104 Zeng, Z. *et al.* Sex-hormone-driven innate antibodies protect females and infants against EPEC infection. *Nat Immunol* **19**, 1100-1111 (2018). <u>https://doi.org:10.1038/s41590-018-0211-2</u>
- 105 Ng-Nguyen, D. *et al.* The epidemiology of Taenia spp. infection and Taenia solium cysticerci exposure in humans in the Central Highlands of Vietnam. *BMC Infect Dis* **18**, 527 (2018). <u>https://doi.org:10.1186/s12879-018-3434-9</u>
- 106 Kelvin, E. A. *et al.* The association of host age and gender with inflammation around neurocysticercosis cysts. *Ann Trop Med Parasitol* **103**, 487-499 (2009). https://doi.org:10.1179/000349809X12459740922291
- 107 Morales-Montor, J. & Larralde, C. The role of sex steroids in the complex physiology of the host-parasite relationship: the case of the larval cestode of Taenia crassiceps. *Parasitology* **131**, 287-294 (2005). <u>https://doi.org:10.1017/s0031182005007894</u>
- 108 Wright, J. E., Werkman, M., Dunn, J. C. & Anderson, R. M. Current epidemiological evidence for predisposition to high or low intensity human helminth infection: a systematic review. *Parasit Vectors* **11**, 65 (2018). <u>https://doi.org:10.1186/s13071-018-2656-4</u>
- 109 Ayabina, D. V. *et al.* Gender-related differences in prevalence, intensity and associated risk factors of Schistosoma infections in Africa: A systematic review and meta-analysis. *PLoS Negl Trop Dis* **15**, e0009083 (2021). <u>https://doi.org:10.1371/journal.pntd.0009083</u>

- 110 Nakazawa, M. *et al.* Schistosoma mansoni: susceptibility differences between male and female mice can be mediated by testosterone during early infection. *Exp Parasitol* **85**, 233-240 (1997). <u>https://doi.org:10.1006/expr.1997.4148</u>
- 111 Bernin, H. & Lotter, H. Sex Bias in the Outcome of Human Tropical Infectious Diseases: Influence of Steroid Hormones. *Journal of Infectious Diseases* **209**, S107-S113 (2014). <u>https://doi.org:10.1093/infdis/jit610</u>
- 112 Hajjeh, R. A., Brandt, M. E. & Pinner, R. W. Emergence of cryptococcal disease: epidemiologic perspectives 100 years after its discovery. *Epidemiol Rev* **17**, 303-320 (1995). <u>https://doi.org:10.1093/oxfordjournals.epirev.a036195</u>
- 113 Shaheen, A. A., Somayaji, R., Myers, R. & Mody, C. H. Epidemiology and trends of cryptococcosis in the United States from 2000 to 2007: A population-based study. *Int J STD AIDS* **29**, 453-460 (2018). <u>https://doi.org:10.1177/0956462417732649</u>
- 114 Acuna-Soto, R., Maguire, J. H. & Wirth, D. F. Gender distribution in asymptomatic and invasive amebiasis. *Am J Gastroenterol* **95**, 1277-1283 (2000). https://doi.org:10.1111/j.1572-0241.2000.01525.x
- 115 Sellau, J. *et al.* Androgens predispose males to monocyte-mediated immunopathology by inducing the expression of leukocyte recruitment factor CXCL1. *Nat Commun* **11**, 3459 (2020). <u>https://doi.org:10.1038/s41467-020-17260-y</u>
- 116 Lockard, R. D., Wilson, M. E. & Rodriguez, N. E. Sex-Related Differences in Immune Response and Symptomatic Manifestations to Infection with Leishmania Species. *J Immunol Res* **2019**, 4103819 (2019). <u>https://doi.org:10.1155/2019/4103819</u>
- 117 Soares, L., Abad-Franch, F. & Ferraz, G. Epidemiology of cutaneous leishmaniasis in central Amazonia: a comparison of sex-biased incidence among rural settlers and field biologists. *Trop Med Int Health* **19**, 988-995 (2014). <u>https://doi.org:10.1111/tmi.12337</u>
- 118 Layegh, P., Moghiman, T. & Ahmadian Hoseini, S. A. Children and cutaneous leishmaniasis: a clinical report and review. *J Infect Dev Ctries* **7**, 614-617 (2013). https://doi.org:10.3855/jidc.2939
- 119 Cloots, K. *et al.* Male predominance in reported Visceral Leishmaniasis cases: Nature or nurture? A comparison of population-based with health facility-reported data. *PLoS Negl Trop Dis* **14**, e0007995 (2020). <u>https://doi.org:10.1371/journal.pntd.0007995</u>
- 120 Layegh, P., Moghiman, T. & Ahmadian Hoseini, S. A. Children and cutaneous leishmaniasis: a clinical report and review. *The Journal of Infection in Developing Countries* **7**, 614-617 (2013). <u>https://doi.org:10.3855/jidc.2939</u>
- 121 Rodriguez, N. E. *et al.* Epidemiological and Experimental Evidence for Sex-Dependent Differences in the Outcome of Leishmania infantum Infection. *Am J Trop Med Hyg* **98**, 142-145 (2018). <u>https://doi.org:10.4269/ajtmh.17-0563</u>
- 122 Kobets, T. *et al.* Genetics of host response to Leishmania tropica in mice different control of skin pathology, chemokine reaction, and invasion into spleen and liver. *PLoS Negl Trop Dis* **6**, e1667 (2012). <u>https://doi.org:10.1371/journal.pntd.0001667</u>
- 123 Bryson, K. J. *et al.* BALB/c mice deficient in CD4 T cell IL-4Ralpha expression control Leishmania mexicana Load although female but not male mice develop a healer phenotype. *PLoS Negl Trop Dis* **5**, e930 (2011). https://doi.org:10.1371/journal.pntd.0000930
- 124 Travi, B. L. *et al.* Gender is a major determinant of the clinical evolution and immune response in hamsters infected with Leishmania spp. *Infect Immun* **70**, 2288-2296 (2002). https://doi.org:10.1128/IAI.70.5.2288-2296.2002
- 125 Oghumu, S. *et al.* Transgenic expression of CXCR3 on T cells enhances susceptibility to cutaneous Leishmania major infection by inhibiting monocyte maturation and promoting a Th2 response. *Infect Immun* **83**, 67-76 (2015). <u>https://doi.org:10.1128/IAI.02540-14</u>

- 126 Lindova, J. *et al.* Gender differences in behavioural changes induced by latent toxoplasmosis. *Int J Parasitol* **36**, 1485-1492 (2006). https://doi.org:10.1016/j.ijpara.2006.07.008
- 127 Roberts, C. W., Cruickshank, S. M. & Alexander, J. Sex-determined resistance to Toxoplasma gondii is associated with temporal differences in cytokine production. *Infect Immun* 63, 2549-2555 (1995). <u>https://doi.org:10.1128/iai.63.7.2549-2555.1995</u>
- 128 Sun, K. S., Tsai, C. F., Chen, S. C., Chen, Y. Y. & Huang, W. C. Galactomannan Testing and the Incidence of Invasive Pulmonary Aspergillosis: A 10-Year Nationwide Population-Based Study in Taiwan. *PLoS One* **11**, e0149964 (2016). <u>https://doi.org:10.1371/journal.pone.0149964</u>
- 129 vom Steeg, L. G. & Klein, S. L. SeXX Matters in Infectious Disease Pathogenesis. *PLoS Pathog* **12**, e1005374 (2016). <u>https://doi.org:10.1371/journal.ppat.1005374</u>
- 130 Schaefer, A. L. *et al.* Factors Contributing to Sex Differences in Mice Inhaling Aspergillus fumigatus. *Int J Environ Res Public Health* **17** (2020). https://doi.org:10.3390/ijerph17238851
- 131 Guess, T. E., Rosen, J., Castro-Lopez, N., Wormley, F. L., Jr. & McClelland, E. E. An inherent T cell deficit in healthy males to C. neoformans infection may begin to explain the sex susceptibility in incidence of cryptococcosis. *Biol Sex Differ* **10**, 44 (2019). https://doi.org:10.1186/s13293-019-0258-2
- 132 Lortholary, O., Improvisi, L., Fitting, C., Cavaillon, J. M. & Dromer, F. Influence of gender and age on course of infection and cytokine responses in mice with disseminated Cryptococcus neoformans infection. *Clin Microbiol Infect* 8, 31-37 (2002). <u>https://doi.org:10.1046/j.1469-0691.2002.00375.x</u>
- 133 Bellissimo-Rodrigues, F., Bollela, V. R., Da Fonseca, B. A. & Martinez, R. Endemic paracoccidioidomycosis: relationship between clinical presentation and patients' demographic features. *Med Mycol* **51**, 313-318 (2013). https://doi.org:10.3109/13693786.2012.714529
- 134 Shankar, J., Restrepo, A., Clemons, K. V. & Stevens, D. A. Hormones and the resistance of women to paracoccidioidomycosis. *Clin Microbiol Rev* **24**, 296-313 (2011). https://doi.org:10.1128/CMR.00062-10
- 135 Pinzan, C. F., Ruas, L. P., Casabona-Fortunato, A. S., Carvalho, F. C. & Roque-Barreira, M. C. Immunological basis for the gender differences in murine Paracoccidioides brasiliensis infection. *PLoS One* **5**, e10757 (2010). https://doi.org:10.1371/journal.pone.0010757
- 136 Shemer, A. & Babaev, M. Fungal Infections (Onychomycosis, Tinea Pedis, Tinea Cruris, Tinea Capitis, Tinea Manuum, Tinea Corporis, different Candida Infections, and Pityriasis Versicolor) and Mycological Laboratory Analyses. (2018).
- 137 d'Enfert, C. *et al.* The impact of the Fungus-Host-Microbiota interplay upon Candida albicans infections: current knowledge and new perspectives. *FEMS Microbiol Rev* **45** (2021). <u>https://doi.org:10.1093/femsre/fuaa060</u>
- 138 Severance, E. G. *et al.* Candida albicans exposures, sex specificity and cognitive deficits in schizophrenia and bipolar disorder. *NPJ Schizophr* **2**, 16018 (2016). <u>https://doi.org:10.1038/npjschz.2016.18</u>