Sex and Infection—Is it Better to be a Woman?

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Conflicts of Interest Disclosure

• none
Sex and gender affect the outcome of infectious diseases

<table>
<thead>
<tr>
<th>Viruses</th>
<th>Intensity</th>
<th>Prevalence or Incidence</th>
<th>Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td></td>
<td></td>
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<tr>
<td>Influenza virus (avian H7N9)</td>
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<tr>
<td>Influenza virus (2009 H1N1)</td>
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<tr>
<td>MERS-CoV</td>
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<tr>
<td>Hepatitis B Virus</td>
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<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Intensity</th>
<th>Prevalence or Incidence</th>
<th>Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Mycobacterium tuberculosis</em></td>
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<tr>
<td><em>Legionella pneumophila</em></td>
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<tr>
<td><em>Campylobacter jejuni</em></td>
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<tr>
<td><em>Leptospira spp.</em></td>
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<table>
<thead>
<tr>
<th>Parasites</th>
<th>Intensity</th>
<th>Prevalence or Incidence</th>
<th>Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Plasmodium falciparum</em></td>
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<tr>
<td><em>Toxoplasma gondii</em></td>
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<td></td>
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<tr>
<td><em>Schistosoma mansoni</em></td>
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<tr>
<td><em>Entamoeba histolytica</em></td>
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<table>
<thead>
<tr>
<th>Fungi</th>
<th>Intensity</th>
<th>Prevalence or Incidence</th>
<th>Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Paracoccidioides brasiliensis</em></td>
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<td></td>
<td></td>
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<tr>
<td><em>Aspergillosis fumigatus</em></td>
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<tr>
<td><em>Cryptococcus neoformans</em></td>
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</tbody>
</table>

= Male Bias  
= No Observed Bias  
= Female Bias  
= Not Determined

Sex differences in the etiology of damage from infectious diseases

Mediators: sex chromosomes, sex hormones, behavior

Disease

Host Damage

Weak

Strong

Immune Response

Sex differences in immune responses over the life course

**Innate immunity**
- Increased inflammatory responses in males
- ↑ Inflammation in males
- ↑ NK cells in males
- ↑ Inflammation in females
- ↑ NK cells in males

**Adaptive immunity**
- Increased IgE levels in males
- CD4/CD8 ratios and CD4+ T cell numbers equal
- CD8+ T cell numbers equal
- IgA levels in males ≥ females
- IgM levels in males ≥ females
- IgG and IgM levels equal
- B cell numbers equal
- Treg cell numbers in males ≥ females
- CD4/CD8 ratios and CD4+ T cells ↑ in females
- CD8+ T cells ↑ in males
- T cell activation/proliferation ↑ in females
- Treg cells ↑ in males
- B cells ↑ in females
- Immunoglobulins ↑ in females

Klein and Flanagan 2016
*Nat Rev Immunol*
FEMALES OF REPRODUCTIVE AGES HAVE MORE SEVERE INFLUENZA
Young women are at greatest risk for severe influenza.

Zarychanski et al. 2010 CMAJ 182:257
The outcome of influenza infection is worse in female mice

Female mice suffer more inflammation during influenza infection

Vermillion et al. unpublished data
Males produce more growth factors associated with repair following infection.

Vermillion et al. unpublished data

DAPI  AREG  beta-Tubulin

Human Alveolar Epithelial Cells
WHAT PROTECTS MALES FROM IMMUNOPATHOLOGY?
Castration of males reduces survival but does not affect influenza replication

Testosterone protects against influenza virus infection

A/PR8

A/ma2009

vom Steeg et al. 2016 AJP Lung
Testosterone reduces pulmonary inflammation in males

vom Steeg et al. 2016 AJP Lung
Testosterone increases pulmonary Treg cells during influenza infection.

vom Steeg et al. 2016 AJP Lung
Males suffer more severe influenza among individuals 65+ years

Wang et al. 2002 Vaccine 20:2494
Treatment of aged male mice with testosterone protects against influenza.
WHAT CAN PROTECT FEMALES?
Progesterone is anti-inflammatory

- Influenza infection disrupts the reproductive cycle in females causing persistent diestrus
- Can hormone replacement therapy improve the outcome of influenza in females?

Hall and Klein 2017 *Mucosal Immunol* in press
Progesterone protects female mice against severe influenza

Hall et al. 2016 PLoS Pathogens 12(9):e1005840
Progesterone increases amphiregulin during influenza infection in female mice

Hall et al. 2016 PLoS Pathogens 12(9):e1005840
Treatment of influenza-infected female mice with progesterone increases cellular proliferation

A

B

C

Hall et al. 2016 PLoS Pathogens 12(9):e1005840
Progesterone treatment improves pulmonary function during influenza infection

Lung diffusing capacity – gas exchange

Hall et al. 2016 PLoS Pathogens 12(9):e1005840
Deletion of AREG reverses the protective effects of progesterone

Hall et al. 2016 PLoS Pathogens 12(9):e1005840
Levonorgestrel also protects females against severe influenza outcome

Hall et al. 2017 J. Virol. 91:e02160-16
VACCINES PROTECT FEMALES
### Sex differences in responses to vaccines in humans

<table>
<thead>
<tr>
<th>Target group</th>
<th>Vaccine</th>
<th>Sex difference in Immune response</th>
<th>Sex difference in adverse reactions</th>
<th>Age (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Children</strong></td>
<td>Hepatitis B</td>
<td>Greater in females</td>
<td>Not defined</td>
<td>&lt;12</td>
</tr>
<tr>
<td></td>
<td>Diphtheria</td>
<td>Greater in females</td>
<td>Not defined</td>
<td>&lt;2</td>
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<tr>
<td></td>
<td>Pertussis</td>
<td>Greater in females</td>
<td>Not defined</td>
<td>&lt;2</td>
</tr>
<tr>
<td></td>
<td>Pneumococcal</td>
<td>Greater in females</td>
<td>Not defined</td>
<td>6–9</td>
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<tr>
<td></td>
<td>Rabies</td>
<td>Greater in females</td>
<td>Not defined</td>
<td>6–9</td>
</tr>
<tr>
<td></td>
<td>Measles</td>
<td>Greater in females or equivalent in both sexes</td>
<td>Increased in females</td>
<td>&lt;3</td>
</tr>
<tr>
<td></td>
<td>RTS,S vaccine against malaria</td>
<td>Greater in females</td>
<td>Increased in females</td>
<td>&lt;2</td>
</tr>
<tr>
<td></td>
<td>Human papillomavirus</td>
<td>Greater in females</td>
<td>Increased in females</td>
<td>5–17</td>
</tr>
<tr>
<td><strong>Adults</strong></td>
<td>Influenza</td>
<td>Greater in females</td>
<td>Increased in females</td>
<td>18–49</td>
</tr>
<tr>
<td></td>
<td>Hepatitis B</td>
<td>Greater in females</td>
<td>Increased in females</td>
<td>&gt;18</td>
</tr>
<tr>
<td></td>
<td>Herpes virus</td>
<td>Greater in females</td>
<td>Increased in females</td>
<td>&gt;18</td>
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<tr>
<td></td>
<td>Yellow fever</td>
<td>Greater in females</td>
<td>Increased in females</td>
<td>&gt;18</td>
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<tr>
<td></td>
<td>Rabies</td>
<td>Greater in females</td>
<td>Not defined</td>
<td>&gt;18</td>
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<tr>
<td></td>
<td>Smallpox</td>
<td>Greater in females</td>
<td>Not defined</td>
<td>&gt;18</td>
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<tr>
<td><strong>Aged adults</strong></td>
<td>Influenza</td>
<td>Greater in females</td>
<td>Increased in females</td>
<td>&gt;65</td>
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<tr>
<td></td>
<td>Td/Tdap</td>
<td>Greater in males</td>
<td>Increased in females</td>
<td>&gt;65</td>
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<tr>
<td></td>
<td>Pneumococcal</td>
<td>Greater in males</td>
<td>Increased in females</td>
<td>&gt;65</td>
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<tr>
<td></td>
<td>Shingles</td>
<td>Not defined</td>
<td>Increased in females</td>
<td>&gt;65</td>
</tr>
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Klein and Flanagan 2016
*Nat Rev Immunol*
Sex differences in response to the seasonal influenza vaccine

Engler et al. 2008 Arch Intern Med 168:2405
Females vaccinated with killed 2009 H1N1 have higher antibody titers than males

Fink and Klein, unpublished data
Vaccinated females are better protected against challenge than males

![Image of HA antigenic site with K166 highlighted]

Figure 1A: HA antigenic site with K166 highlighted.

Figure 1B: Fraction of pH1N1 isolates with K166 from 2009 to 2013.

Figure 2: Changes in body temperature and body mass over time for males and females post challenge.

Fink and Klein, unpublished data
Adult females develop higher antibody responses to \textit{P.f. CSP}

Vaccinate with 100,000 irradiated \textit{P.b.-P.f. CSP} sporozoites

Vom Steeg, Garcia, Zavala, & Klein, unpublished data
Adult females are better protected against parasite challenge.

Mosquito bite challenge (P.b.-P.f. CSP infected A. stephensi)
Sex differences in the etiology of damage from infection

Mediators: sex chromosomes, sex hormones, behavior

Disease

Vaccination

Induce repair

Repair Regulation

Host Damage

Low

High

Weak

Strong

Immune Response

♂ Bias

♀ Bias

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- Dr. Jeff Mogil & Dr. Julie Côté