Sex-based Differences in Infectious Disease Pathogenesis and Immunity

Prof. Marylyn M. Addo
MD, PhD, MSc, DTM&H
Take home message
Take home message
Take home message 2

SEX ≠ GENDER
Overview

• Sex differences in immunity
• Sex differences in infectious diseases
  – Parasitic infections
  – Viral infections
• Sex differences in vaccinations
Overview

- Sex differences in immunity
Most autoimmune diseases affect women

Why ????

Figure 2 | Sex distribution of the most important autoimmune diseases. The depicted diseases are the ones which usually show female predominance. \(^{21,102}\)
Sex matters in immunity

[Diagram showing the relationships between sex chromosomes, indirect effects of sex chromosomes (e.g., hormones), epigenetic modifications, immune cell phenotypes, microbiome, and sex-specific exposure to environmental factors.]
Sex matters in immunity
### Genes coded on the X chromosome

**a Receptors & associated proteins**

- AR: Androgen receptor
- AGTR2: Angiotensin receptor 2
- CSF2RA: Colony-stimulating factor 2 receptor α (granulocyte-macrophage)
- CYSLTR1: Cysteinyl leukotriene receptor 1
- IL-1RAP: Interleukin-1 (IL-1) receptor accessory protein-like 1
- IL-1RAP2: IL-1 receptor accessory protein-like 2
- IL-2RG: IL-2 receptor γ-chain
- IL-3RA: IL-3 receptor α-chain
- IL-9R: IL-9 receptor
- IL-13RA1: IL-13 receptor α1-chain
- IL-13RA2: IL-13 receptor α2-chain
- IRAK: IL-1 receptor-associated kinase
- NGFRAP1: Nerve-growth-factor receptor associated protein 1
- TLR7: Toll-like receptor 7
- TLR8: Toll-like receptor 8

**b Immune-response related proteins**

- XSCID: X-linked severe combined immunodeficiency
- ELK1: Involved in B-cell development
- EPAG: Early lymphoid activation protein
- GATA1: GATA-binding protein 1
- GTD: Gonadotropin deficiency
- IIDD: X-linked susceptibility to insulin-dependent diabetes
- IG8PI: CD99 antigen immunoglobulin binding protein 1
- IG8F1: Immunoglobulin superfamily member 1
- ITGB1BP2: Integrin-β1-binding protein 2
- CD99: Also known as MIC2; associated with T-cell function
- MTCPI: Mature T-cell proliferation 1
- PFC: Properdin P factor, complement
- TIMP1: Tissue inhibitors of metalloproteinase 1
- CD40L: CD40 ligand
- Z391G: An immunoglobulin superfamily protein

**c Transcriptional & translational control effectors**

- RHOGAP: RAS homologue (RHO) GTPase activating proteins 4, 6
- CDC42GEF: Cell-division cycle 42 guanine-nucleotide-exchange factors 6, 9
- ETK: Also known as BMX
- BTK: Bruton agammaglobulinaemia tyrosine kinase
- CDX4: Caudal homeobox transcription factor 4
- TRAP170: A co-factor for SPI transcription factor activation
- DUSP: Dual specificity phosphatases 9, 21
- EEF: Eukaryotic translation elongation factors 1α3, β4
- GAB3: Growth-factor-receptor-bound protein 2-associated binding protein 3
- HDAC: Histone deacetylases 6, 8
- IKKγ: IkB kinase γ, also known as NEMO
- MAP4K15: Mitogen-activated protein kinase kinase kinase kinase 15
- NFκB: Nuclear factor-kB (NF-kB) repressing factor
- NIK: NF-κB-inducing kinase-related kinase
- NFX: Nuclear RNA export factors 2, 3, 4, 5
- PAK3: p21 [also known as CDKN1A]-activated kinase 3
- PKC: Protein kinases 1, 2a, 6
- PRKCI: Protein kinase Ci
- S6K: Ribosomal protein S6 kinase
- SWI/SNF: SWI/SNF-related, matrix associated, actin-dependent regulator of chromatin
- STK9: Serine/threonine kinase 9
- TAF1: TATA-box-binding protein-associated factor 1, TRID subunit
- UBE1: Ubiquitin-activating enzyme E1
- UBE2A: Ubiquitin-conjugating enzyme E2A
- USP: Ubiquitin-specific proteases 9a, 11, 26, 27, 51
- WASP: Wiskott-Aldrich syndrome protein

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*Fish, Nat Rev Imm 2008*
Sex matters in immunity

Indirect effects of the sex chromosomes (e.g., hormones)

Epigenetic modifications

Immune cell phenotypes

Microbiome

Chemical structure of a sex hormone
Sex matters in immunity

Oestrogen receptors are expressed by many immune cells.

Oestrogen and progesterone effects on T-cell responses during menstrual cycle.

Fish, Nat Rev Immunol 2008
Sex matters in immunity

- Stronger immunity in response to pathogens
- Stronger immunity in response to vaccines
- More autoimmunity
Overview

• Sex differences in immunity

• Sex differences in infectious diseases
Overview

• Sex differences in immunity

• Sex differences in infectious diseases
  – parasitic infections
  – viral infections
### Sex differences in parasitic infections

**Table 1. Sex-Biased Tropical Diseases and the Effect of Steroid Hormones on Disease and Immune Response**

<table>
<thead>
<tr>
<th>Tropical Disease</th>
<th>Pathogen(s)</th>
<th>Sex-Associated Bias in Humans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amebiasis</td>
<td><em>Entamoeba histolytica</em>, protozoan parasite</td>
<td>M &gt; F</td>
</tr>
<tr>
<td>Malaria</td>
<td><em>Plasmodium species</em>, protozoan parasites</td>
<td>M &gt; F</td>
</tr>
<tr>
<td>Leishmaniasis</td>
<td><em>Leishmania species</em>, protozoan parasites</td>
<td>M &gt; F</td>
</tr>
<tr>
<td>Toxoplasmosis</td>
<td><em>Toxoplasma gondii</em>, protozoan parasite</td>
<td>F &gt; M</td>
</tr>
<tr>
<td>Schistosomiasis</td>
<td><em>Schistosoma species</em>, parasitic worms</td>
<td>M &gt; F</td>
</tr>
<tr>
<td>Paracoccidioidomycosis</td>
<td><em>Paracoccidioides brasiliensis</em>, fungus</td>
<td>M &gt; F</td>
</tr>
</tbody>
</table>
Amoebic liver abscess (ALA)
Sex differences in Amebiasis

Men are more frequently presenting with amoebic liver abscess despite higher parasite burden in women (Hue, Vietnam)
Sex differences in Amebiasis

Sex dimorphism in mice

<table>
<thead>
<tr>
<th>days p.i.</th>
<th>abscess score</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>21</td>
<td>***</td>
</tr>
<tr>
<td>35</td>
<td>***</td>
</tr>
</tbody>
</table>

Male: ♂
Female: ▲

* p < 0.05
** p < 0.01
*** p < 0.001
Sex differences in Amebiasis

testosterone substitution in female mice enhances amoebic abcess formation

ovariectomy (ovx), orchiectomy (ox)  implantation of hormone/placebo pellets
infection  analysis

age of mice (weeks)

serum testosterone level (ng/ml)

p<0.0001

female placebo  testosterone substituted female  male

abscess score

p<0.05  p<0.05

female ovx placebo  female ovx testosterone  female placebo  female testosterone

parasite load

p<0.02  p<0.0002

female ovx placebo  female ovx testosterone  female placebo  female testosterone

provided by Hanna Lotter, BNI
Overview

• Sex differences in immunity

• Sex differences in infectious diseases
  – parasitic infections
  – viral infections
Sex differences in viral infections

Klein, SL (2012) Bioessays

© by author
Sex, gender and influenza
## Sex differences in Influenza

<table>
<thead>
<tr>
<th>Dependent measure</th>
<th>Influenza</th>
<th>Virus</th>
<th>Sex difference&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Study population&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Study country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morbidity/</td>
<td>Seasonal</td>
<td>H3N2/</td>
<td>F &gt; M</td>
<td>Elderly</td>
<td>Portugal</td>
</tr>
<tr>
<td>mortality</td>
<td></td>
<td>H1N1</td>
<td>M &gt; F</td>
<td>Elderly</td>
<td>Switzerland</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>45+</td>
<td>USA</td>
</tr>
<tr>
<td></td>
<td>Pandemic</td>
<td>H2N2</td>
<td>F &gt; M</td>
<td>1-144</td>
<td>USA</td>
</tr>
<tr>
<td></td>
<td>Epidemic</td>
<td>H2N2</td>
<td>M &gt; F</td>
<td>45+</td>
<td>USA</td>
</tr>
<tr>
<td></td>
<td>Outbreak</td>
<td>H5N1</td>
<td>F &gt; M</td>
<td>After puberty to adults</td>
<td>Egypt, Indonesia</td>
</tr>
<tr>
<td></td>
<td>Pandemic</td>
<td>1918</td>
<td>M &gt; F</td>
<td>Adults</td>
<td>China, Viet Nam</td>
</tr>
<tr>
<td></td>
<td></td>
<td>H1N1</td>
<td>M = F</td>
<td>After puberty</td>
<td>Australia, Denmark, Finland, France, Italy, the Netherlands, New Zealand, Norway, Spain, Sweden, Switzerland, the United Kingdom, USA</td>
</tr>
<tr>
<td></td>
<td>2009</td>
<td>H1N1</td>
<td>F &gt; M</td>
<td>Adults</td>
<td>South Africa</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>M &gt; F</td>
<td>Adults</td>
<td>Australia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>M = F</td>
<td>Adults</td>
<td>Brazil, Peru</td>
</tr>
</tbody>
</table>
Females had more severe disease courses during the 2009 H1N1 Pandemic

Zarychanski et al. 2010 CMAJ 182:257
Pregnant women have a higher risk for severe disease courses in influenza

WHO 2010
Morbidity and mortality from maH1N1 influenza virus infection is greater in female mice

...and Hepatitis C
Sex differences in HCV infections

Men present more frequently with HCV-induced liver cirrhosis

Davis et al, Gastroenterology 2010
**Sex differences in HCV infections**

- **Greater likelihood of spontaneous clearance of acute HCV infection in women than in men**

- **Higher symptom burden in HIV–HCV coinfected women**

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**Hepatitis**

Higher clearance of hepatitis C virus infection in females compared with males

I Bakr, C Rekacewicz, M El Hosseiny, S Ismail, M El Daly, S El-Kafrawy, G Esmat, M A Hamid, M K Mohamed, A Fontanet

Factors associated with spontaneous clearance of hepatitis C virus among illicit drug users

Jason Grebely BSc PhD, Jesse D Raffa BSc MSc, Calvin Lai MMath, Mel Krajden MD FRCP C, Brian Conway MD FRCP C, Mark W Tyndall MD ScD FRCP C


Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies

Grebely J, Raffa JD, Lai C, Krajden M, Conway B,

Female Sex and IL28B, a Synergism for Spontaneous Viral Clearance in Hepatitis C Virus (HCV) Seroconverters from a Community-Based Cohort

Charlotte H. B. S. van den Berg, Bart P. X. Grady, Janke Schinkel, Thijs van de Laar, Richard Molenkamp, Robin van Houdt, Roel A. Coutinho, Debbie van Baarle, Maria Prins
Sex differences in HCV infection

Female sex has been reported as an independent predictor of clearance in a cohort of individuals with acute HCV with various modes of transmission.

Grebely J et al; Hepatology 2014;59:109-120
...in HIV infection
South Africa: 'Over 25% of schoolgirls HIV positive'

High HIV-1 infection rates in young pregnant women in Umlazi, Durban, South Africa
Sex differences in HIV-1 infection

"Proportional-hazards models showed that women with the same viral load as men had a 1.6-fold higher risk of AIDS (95% CI=1.10–2.32); or, equivalently, that women with half the viral load of men had a similar time to AIDS as men."

also: Sterling/Quinn NEJM 2001
Sex differences in HIV-1 infection

Proportional-hazards models showed that women with the same viral load as men had a 1.6-fold higher risk of AIDS (95% CI = 1.10–2.32); or, equivalently, that women with half the viral load of men had a similar time to AIDS as men.

also: Sterling/Quinn NEJM 2001
Dendritic cells from women produce more IFNα in response to TLR7 stimulation than pDCs from men.
Stronger IFN-α production by pDCs from women following stimulation with HIV-1-derived TLR7/8 ligands

![Flow cytometry histogram](image)

**Unstimulated**

- Male: 0%
- Female: 0%

**+gagRNA1166**

- Male: 13.5%
- Female: 49%

*Courtesy of M. Altfeld*
Stronger IFN-α production by pDCs from women following stimulation with HIV-1-derived TLR7/8 ligands

**TLR7/8**
- GagRNA1166: p = 0.006
- gp160RNA2093: p = 0.02

**TLR9**
- ODN02216: p = 0.7

Meier/Chang et al, Nat Med 2009
Hypothesis:

Stronger immune activation in women mediated by stronger responses to HIV-1-encoded TLR7/8 ligands might result in faster HIV-1 disease progression in women compared to men for the same VL.
Study of Immune Activation in HAART naïve women and men from ACTG 384

Meier/Chang et al, Nat Med 2009
Conclusions

IFNα is protective in viral infections:
• might explain better HCV clearance rate in women?

IFNα can induce excessive inflammation:
• Might explain more severe Influenza disease in women?
Overview

• Sex differences in immunity
• Sex differences in viral infections
• Sex differences in vaccinations
Yellow Fever Vaccine

• Live, attenuated virus

• One of the most effective vaccines
  – Neutralizing antibodies can be detected in >95% of persons vaccinated
  – Vaccine efficacy is estimated at 85%

• Immune response
  – Induces cytotoxic T lymphocytes
  – Induces neutralizing antibodies that can persist for decades
More genes are differentially regulated in women following YFV 17D vaccination than in men.
Table 1: Sex differences in response to both childhood and adult virus vaccines

<table>
<thead>
<tr>
<th>Vaccine Type</th>
<th>Sex Difference</th>
<th>Age of Study Population</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rate of vaccination</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPV, LAIV</td>
<td>F&gt;M</td>
<td>&gt;18 years</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>M&gt;F</td>
<td>&gt;18 years</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>All ages</td>
<td>9</td>
</tr>
<tr>
<td>MMR</td>
<td>F&gt;M</td>
<td>6-55 months</td>
<td>10</td>
</tr>
<tr>
<td><strong>Rate of seroconversion</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAV, HBV</td>
<td>F&gt;M</td>
<td>&gt;18 years</td>
<td>11</td>
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<tr>
<td></td>
<td>F&gt;M</td>
<td>&gt;65 years</td>
<td>12</td>
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<tr>
<td><strong>Humoral immune response</strong></td>
<td></td>
<td></td>
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<tr>
<td>IPV</td>
<td>F&gt;M</td>
<td>&gt;18 years</td>
<td>13-15</td>
</tr>
<tr>
<td></td>
<td>F&gt;M</td>
<td>&gt;65 years</td>
<td>16-18</td>
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<tr>
<td>S/DIV</td>
<td>F&gt;M</td>
<td>&gt;18 years</td>
<td>19</td>
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<tr>
<td>BERA27/3, KAI, AREX, YF-17D</td>
<td>M&gt;F</td>
<td>&gt;18 years</td>
<td>20, 21</td>
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<tr>
<td>AIP-YF, IBDU</td>
<td>F&gt;M</td>
<td>&gt;18 years</td>
<td>21, 22</td>
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<tr>
<td>RA27/3</td>
<td>M&gt;F</td>
<td>10-17 years</td>
<td>23</td>
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<td><strong>Schwarz</strong></td>
<td>F&gt;M</td>
<td>&gt;18 years</td>
<td>24</td>
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<tr>
<td>MMR</td>
<td>F&gt;M</td>
<td>5-10 years</td>
<td>25</td>
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<td></td>
<td>F&gt;M</td>
<td>10-17 years</td>
<td>26</td>
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<td></td>
<td>F&gt;M</td>
<td>10-17 years</td>
<td>27, 28</td>
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<td>HPV4</td>
<td>M&gt;F</td>
<td>5-12 years</td>
<td>29</td>
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<td>HAV</td>
<td>F&gt;M</td>
<td>&gt;18 years</td>
<td>30-32</td>
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<td></td>
<td>F&gt;M</td>
<td>6 months to 17 years</td>
<td>34, 35</td>
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<td>HBV</td>
<td>F&gt;M</td>
<td>&gt;18 years</td>
<td>36-39</td>
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<td>HAV, HBV</td>
<td>F&gt;M</td>
<td>&gt;18 years</td>
<td>40-41</td>
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<td>HSV-2 gD</td>
<td>F&gt;M</td>
<td>&gt;18 years</td>
<td>42, 43</td>
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<td>HDV, PCECV</td>
<td>F&gt;M</td>
<td>&gt;18 years</td>
<td>44-45</td>
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<td>Dryvax</td>
<td>F&gt;M</td>
<td>&gt;18 years</td>
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<td>Attenuated Dengue virus</td>
<td>F&gt;M</td>
<td>&gt;18 years</td>
<td>47</td>
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<td>Attenuated Venezuelan equine encephalitis virus</td>
<td>M&gt;F</td>
<td>&gt;18 years</td>
<td>48</td>
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<td><strong>Cell mediated immunity</strong></td>
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<tr>
<td>MMR</td>
<td>F&gt;M</td>
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<td>21, 28</td>
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<td>RA27/3</td>
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<td>10-17 years</td>
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<td>HSV-2 gD</td>
<td>F&gt;M</td>
<td>&gt;18 years</td>
<td>49</td>
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<td><strong>Adverse reaction</strong></td>
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<td>IPV</td>
<td>F&gt;M</td>
<td>&gt;18 years</td>
<td>14, 50-51</td>
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<td></td>
<td>F&gt;M</td>
<td>&gt;65 years</td>
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<td>54</td>
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<tr>
<td>MMR</td>
<td>F&gt;M</td>
<td>6-55 months</td>
<td>55</td>
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<tr>
<td></td>
<td>M&gt;F</td>
<td>6-55 months</td>
<td>56</td>
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<tr>
<td></td>
<td>F&gt;M</td>
<td>5-10 years</td>
<td>57</td>
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<tr>
<td>Attenuated Japanese encephalitis virus</td>
<td>F&gt;M</td>
<td>&gt;18 years</td>
<td>58</td>
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<tr>
<td><strong>Mortality</strong></td>
<td></td>
<td></td>
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<tr>
<td>Edmonton-Zagreb</td>
<td>F&gt;M</td>
<td>6-55 months</td>
<td>59</td>
</tr>
</tbody>
</table>

**Table 1:** Sex differences in response to both childhood and adult virus vaccines.
GLYCOPEPTIDE-D-ADJUVANT VACCINE TO PREVENT GENITAL HERPES

LAWRENCE R. STANBERRY, M.D., PH.D., SPOTSWOOD L. SERVANCE, M.D., ANTHONY L. CUNNINGHAM, M.D., DAVID I. BERNSTEIN, M.D., ADRIAN MINDEL, M.D., STEPHEN SACKS, M.D., STEPHEN TYRING, M.D., PH.D., FRED. Y. AOKI, M.D., MONCEF SLAQUI, PH.D., MARTINE DENIS, PH.D., PIERRE VANDEPAPELIERE, M.D., AND GARY DUBIN, M.D., FOR THE GLAXOSMITHKLINE HERPES VACCINE EFFICACY STUDY GROUP*

A

All Subjects

Percentage without Disease

0 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30

Month of Observation

Vaccine group

Control group

Sex differences in Influenza Vaccine Responses

Systems analysis of sex differences reveals an immunosuppressive role for testosterone in the response to influenza vaccination

David Furman\textsuperscript{a,1,2,3}, Boris P. Hejblum\textsuperscript{b,1}, Noah Simon\textsuperscript{c}, Vladimir Joje\textsuperscript{d}, Cornelia L. Dekker\textsuperscript{e}, Rodolphe Thiébaut\textsuperscript{b}, Robert J. Tibshirani\textsuperscript{c,f}, and Mark M. Davis\textsuperscript{a,g,h,3}

PNAS | January 14, 2014 | vol. 111 | no. 2 | 869–874
Summary: Sex matters in immunity

Markle & Fish (2014) TRENDS Immunol
Immune Cells Have Sex and So Should Journal Articles

Sabra L. Klein

The W. Harry Feinestone Department of Molecular Microbiology and Immunology, Department of Biochemistry and Molecular Biology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland 21205

Klein (2012) Endocrinology

Sex bias in trials and treatment must end

Gender inequalities in biomedical research are undermining patient care. In the first of three related pieces, Alisan M. Kim, Candace M. Tingen and Teresa K. Woodruff call on journals, funding agencies and researchers to give women parity with men, in studies and in the clinic.
SEX DIFFERENCES IN THE MANIFESTATIONS OF INFECTIOUS DISEASES

S79  Sex Differences in Infectious Diseases—Common but Neglected
Jan van Lunzen and Marcus Altfeld

S81  Natural History and Management of Hepatitis C: Does Sex Play a Role?
Rachel Bascen, Jurgen K. Rockstroh, and Maria Buti

S86  Sex-Based Differences in HIV Type 1 Pathogenesis
Marylyn M. Asbo and Marcus Altfeld

S93  Sex, Immunity and Influenza
Julia Gabrielle and Petra Clara Arck

S100 Biological Differences Between the Sexes and Susceptibility to Tuberculosis
Shepherd Nhamoyebonde and Alasdair Leslie

S107 Sex Bias in the Outcome of Human Tropical Infectious Diseases:
Influence of Steroid Hormones
Hannah Bernin and Hanna Lotter

S114 Sex-based Biology and the Rational Design of Influenza Vaccination Strategies
Sabine L. Klein and Andrew Pakosz

S120 Sex Differences in Pediatric Infectious Diseases
M. Muenchhofer and Philip J. R. Gauldor
These observations should influence our thinking, research and ultimately inform our clinical practice... and lead to =>

“personalized medicine”
Acknowledgements

- Addo lab members
- Marcus Altfeld and lab team

Funders:
- DZIF
- Wellcome Trust
- BMG/BMBF
Thank you for your time and attention!

Marylyn M. Addo m.addo@uke.de
Sex differences in RSV infection

**RSV Burden of Disease**

- 34,000,000 patients
- 3,400,000 hospitalizations
- 253,000 deaths

provided by L. Bont, UMC
# Sex differences in RSV infection

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>boys</th>
<th>%</th>
<th>Journal</th>
<th>Year</th>
</tr>
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<tbody>
<tr>
<td>Paynter</td>
<td>231</td>
<td>144</td>
<td>62.3%</td>
<td>PIDJ</td>
<td>2014</td>
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<tr>
<td>Blanken</td>
<td>129</td>
<td>68</td>
<td>52.7%</td>
<td>PLOS One</td>
<td>2013</td>
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<td>Hennus</td>
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<td>11</td>
<td>61.1%</td>
<td>PLOS One</td>
<td>2013</td>
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<td>Van Woensel</td>
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Prediction of Immunogenicity of Yellow Fever Vaccine

• Pulendran and colleagues used a biologic systems approach to evaluate and then predict the response to the yellow fever vaccine.

• A total of 25 healthy people were immunized in 2 independent trials

• Measured innate immune response, CD8+ T cell responses, and antibody titers

• Performed transcriptional profiling of peripheral blood mononuclear cells

• Employed a sophisticated algorithm to identify key gene signatures that predict CD8+ T cell response from the early transcriptome data

• Potential tool for the prediction of vaccine-induced immune response and forward assessment of vaccine efficacy
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• Potential tool for the prediction of vaccine-induced immune response and forward assessment of vaccine efficacy

• Demonstration that YF-mediated activation of TLRs and TLR signaling genes was associated with strength of adaptive immunity to YF vaccine