Improving the Efficacy of Vaccinations for Women, Children, and Men

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Causes of global deaths differ between males and females (15-49 years)

Lozano et al. 2012 Lancet 380:2095

3,496,480 total deaths
5,741,344 total deaths
The outcome of viral infections differ between males and females

<table>
<thead>
<tr>
<th>Virus</th>
<th>Dependent measure</th>
<th>Sex-specific difference</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytomegalovirus</td>
<td>P</td>
<td>$M &lt; F$</td>
<td>[14]</td>
</tr>
<tr>
<td>Dengue virus</td>
<td>P</td>
<td>$M &gt; F$</td>
<td>[106]</td>
</tr>
<tr>
<td>Epstein Barr virus</td>
<td>D</td>
<td>$M &gt; F$</td>
<td>[107]</td>
</tr>
<tr>
<td>Hantaviruses (multiple species)</td>
<td>P</td>
<td>$M &gt; F$</td>
<td>[108]</td>
</tr>
<tr>
<td>Hepatitis B virus</td>
<td>I, P, D</td>
<td>$M &gt; F$</td>
<td>[61, 64, 65, 67]</td>
</tr>
<tr>
<td>Hepatitis C virus</td>
<td>P, I</td>
<td>$M &gt; F$</td>
<td>[70, 71]</td>
</tr>
<tr>
<td>Herpes simplex virus type 2</td>
<td>I, P</td>
<td>$M &lt; F$</td>
<td>[48, 109]</td>
</tr>
<tr>
<td>Human immunodeficiency virus (HIV)</td>
<td>I</td>
<td>$M &gt; F$</td>
<td>[32, 33, 37]</td>
</tr>
<tr>
<td>Human T-cell leukemia virus Type 1</td>
<td>D</td>
<td>$M &lt; F$</td>
<td></td>
</tr>
<tr>
<td>Influenza A viruses</td>
<td>D, M</td>
<td>$M &lt; F$</td>
<td>[86, 88, 89]</td>
</tr>
<tr>
<td>Measles</td>
<td>M</td>
<td>$M &lt; F$</td>
<td>[111]</td>
</tr>
<tr>
<td>West Nile virus</td>
<td>I</td>
<td>$M &gt; F$</td>
<td>[112]</td>
</tr>
</tbody>
</table>

$P =$ prevalence; $I =$ intensity; $D =$ disease; $M =$ mortality
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Effectors</th>
<th>Days after virus exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magnitude of response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Innate immune response</td>
<td>PRRs</td>
<td>0</td>
</tr>
<tr>
<td>Antigen recognition</td>
<td>APCs</td>
<td>7</td>
</tr>
<tr>
<td>Lymphocyte activation</td>
<td>cytokines</td>
<td>14</td>
</tr>
<tr>
<td>Virus elimination by</td>
<td>chemokines</td>
<td>21</td>
</tr>
<tr>
<td>the adaptive immune</td>
<td>cells and effector</td>
<td></td>
</tr>
<tr>
<td>response</td>
<td>T cells</td>
<td></td>
</tr>
<tr>
<td>Return to homeostasis</td>
<td>Regulatory responses</td>
<td></td>
</tr>
</tbody>
</table>

- **PRRs**: Pattern Recognition Receptors
- **APCs**: Antigen呈递细胞
- **cytokines**: 细胞因子
- **chemokines**: 化学因子
- **clonal expansion and differentiation of antibody producing cells and effector T cells**: 克隆扩增和抗体产生细胞及效应T细胞的分化
- **antibody production CD4+ T cell responses**: 抗体产生CD4+ T细胞反应
- **CD8+ T cell responses**: CD8+ T细胞反应

SEX DIFFERENCES IN IMMUNE RESPONSES AND THE OUTCOME OF INFECTION
Correlates of severe 2009 H1N1 disease in young adults

Zarychanski et al. 2010 CMAJ 182:257
Morbidity and mortality from influenza A virus infection is greater in females

Robinson, Lorenzo, Jian, & Klein 2011, PLoS Pathogens, 7:e1002149
Females have a greater induction of cytokines and chemokines in their lungs than males

Robinson, Lorenzo, Jian, & Klein 2011, PLoS Pathogens, 7:e1002149
The responses to viral vaccines differ between males and females

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Humoral response</th>
<th>Adverse reactions</th>
<th>Age (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIV</td>
<td>F &gt; M</td>
<td>F &gt; M</td>
<td>18-65+</td>
</tr>
<tr>
<td>MMR</td>
<td>F &gt;/= M</td>
<td>F &gt; M</td>
<td>&lt; 3</td>
</tr>
<tr>
<td>HBV</td>
<td>F &gt; M</td>
<td>?</td>
<td>&gt; 18</td>
</tr>
<tr>
<td>HSV-2</td>
<td>F &gt; M</td>
<td>?</td>
<td>&gt; 18</td>
</tr>
<tr>
<td>YFV</td>
<td>F &gt; M</td>
<td>F &gt; M</td>
<td>&gt; 18</td>
</tr>
<tr>
<td>HPV</td>
<td>F &gt; M</td>
<td>F &gt; M</td>
<td>5-17</td>
</tr>
<tr>
<td>HIV</td>
<td>?</td>
<td>F &gt; M</td>
<td>&gt; 18</td>
</tr>
<tr>
<td>Rabies</td>
<td>F &gt; M</td>
<td>?</td>
<td>&gt; 18</td>
</tr>
<tr>
<td>Smallpox</td>
<td>F &gt; M</td>
<td>?</td>
<td>&gt; 18</td>
</tr>
<tr>
<td>Dengue</td>
<td>F &gt; M</td>
<td>?</td>
<td>&gt; 18</td>
</tr>
</tbody>
</table>

Klein et al. 2010 *Lancet ID* 10:338
CHILD MORTALITY FOLLOWING VACCINATION IN DEVELOPING COUNTRIES IS HIGHER AMONG GIRLS
Mortality Following the High-Titer Measles Vaccine was Higher Among Girls, Bissau 1986-1990

EZ = Edmonston-Zagreb high-titer measles vaccination

Aaby et al. 1993 J Pediatr 122:904
Should Vaccine Schedules Differ for Boys and Girls?

(Aaby et al. 1993 Lancet 361:2183)

HTMV = high-titer measles vaccine
DTP = diphtheria-tetanus-pertussis
IPV = inactivated poliovirus

F-M mortality ratio = 0.83 (0.41-1.67) for HTMV only
F-M mortality ratio = 2.22 (1.04-4.71) for HTMV + DTP/IPV

(Aaby et al. 1993 Lancet 361:2183)
INFLAMMATORY RESPONSES TO VACCINES ARE HIGHER IN WOMEN
Yellow fever vaccine induces integrated multilineage and polyfunctional immune responses

Take home message: activity along toll-like receptor/inflammatory pathways predicts long-term protection
Females develop higher inflammatory responses to the yellow fever vaccine

Klein et al. 2010 *Lancet* ID 10:338
ANTIBODY RESPONSES AND CROSS PROTECTION ARE HIGHER IN WOMEN FOLLOWING VACCINATION
Current Influenza Vaccines

- **Trivalent inactivated vaccine (TIV):** Killed virus vaccine, given as an intramuscular injection, and typically recommended for children 6 months to 2 years of age and older adult over 65 years of age.

- **High dose TIV:** recommended for older adults over 65 years of age.

- **Live attenuated influenza vaccine (LAIV):** contains weakened live virus that is administered into the nostrils and induces greater immunity than TIV to influenza.

Local Erythema/Induration following TIV is Greater in Females

Cate et al. 1983 Rev Infect Dis 5:737
Sex differences in response to the seasonal influenza vaccine

(Engler et al. 2008 Arch Intern Med 168:2405)
Sex differences in response to TIV among older adults

- Women > 65 also develop higher antibody responses to high-dose and standard-dose TIV in Phase I and III clinical trials;
- Women > 65 report two times more side effects than males to the standard dose TIV;
- Women > 65 also are significantly more likely to report adverse events (e.g., myalgias and pain) following TIV.

October 28, 2009

OP-ED CONTRIBUTORS

Do Women Need Such Big Flu Shots?

By SABRA L. KLEIN and PHYLLIS GREENBERGER

The emergence of the H1N1 swine flu has added urgency to what has become an annual ritual for millions of Americans: getting a flu shot. The good news is that scientists have developed a vaccine against the H1N1 virus. But it is taking much longer than expected to produce the hundreds of millions of doses the government had planned to distribute. And it is still too soon to know how effective the vaccine will be in preventing swine flu.

In all likelihood, we'd have a better H1N1 vaccine — and more of it — if in our preparations we had accounted for the biological differences between men and women.
Females have higher neutralizing antibody titers against influenza A viruses

H1N1 (PR8)  
H3N2 (HK68)

Lorenzo et al. 2011 Vaccine 29:9246
Females are better protected against lethal influenza challenge

Immunize with sublethal H3N2 (day 0)

Measure antibody (day 14-28)

Infect with lethal H1N1 (day 49)

Measure morbidity and virus titers (day 49-56)

Lorenzo et al. 2011 Vaccine 29:9246
Women are less likely to accept influenza vaccines

VACCINE EFFICACY IS HIGHER IN WOMEN
Glycoprotein D-Adjuvant Vaccine Prevents Genital Herpes in Women, but not Men

Phase III trials showed no overall efficacy, but noted substantial differences in the efficacy between women and men.

(Stanberry et al. 2002 N Engl J Med 347:1652)
How to overcome sex-based differences in subunit HSV vaccines

- Focus on viral immune evasion strategies
- Neutralizing antibody, complement, and T-cell responses
- HSV seropositive women have more T cells and stronger IFN-γ production by T cells to gD peptides

Figure 1. Subunit vaccine. This illustration shows a glycoprotein subunit vaccine administered through a syringe into the oro-facial pathway inducing an accessory cell to elicit a T cell response. The antigen presentation will cause these cells to become either CD4+ cells or CD8+ cells. These will then act against HSV, which has established latency in the trigeminal or cervical ganglia.

Coleman & Shukla 2013 Hum Vaccin Immunother 9:1
Sex-specific rational design of vaccines

Klein & Pekosz JID in press