Immune Responses to Human Papillomavirus Vaccines: What We Have Learned

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HPV

- Non-enveloped double-stranded DNA virus
- One of the most common sexually transmitted infections
- >100 types identified
- ~30–40 mucosal
  - ~15–20 oncogenic types
    - HPV 16 and HPV 18 types account for 70% of cervical cancer cases
- Nononcogenic types
  - HPV 6 and 11 are most often associated with external anogenital warts
Most Common Cancers in Women

Breast
Cervix
Ovary
Endometrium
Colon/rectum
Lung
Stomach

More developed countries
Less developed countries

Annual number of cases (thousands)

600 400 200 0 200 400 600

Adapted from Parkin et al, Eur J Cancer 2001; 37 S4
Cervical Pathogenesis

HPV persistence is the most important predictor of high grade cervical cancer precursors.
HPV Causes More than Cervical Cancer

- Cervical Cancer: ~100%
- Penile Cancer: 45%
- Vulvar Cancer: ~40%
- Head & Neck Cancer: 12-70%
- Vaginal Cancer: 60-90%
- Genital Warts: ~100%
- Anal Cancer: 80%+
## HPV Associated Cancers, both Sexes, US 2005-2009

<table>
<thead>
<tr>
<th>Location</th>
<th>Average annual number of cases</th>
<th>HPV attributable</th>
<th>HPV 16/18 attributable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervix</td>
<td>11,279</td>
<td>10,150</td>
<td>7,470</td>
</tr>
<tr>
<td>Vagina</td>
<td>694</td>
<td>520</td>
<td>380</td>
</tr>
<tr>
<td>Vulva</td>
<td>3,039</td>
<td>2,100</td>
<td>1,480</td>
</tr>
<tr>
<td>Anus</td>
<td>3,084</td>
<td>2,810</td>
<td>2,450</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>2,317</td>
<td>1,670</td>
<td>1,420</td>
</tr>
<tr>
<td><strong>Total (Females)</strong></td>
<td><strong>21,342</strong></td>
<td><strong>17,250</strong></td>
<td><strong>13,200</strong></td>
</tr>
<tr>
<td>Penis</td>
<td>1,003</td>
<td>630</td>
<td>450</td>
</tr>
<tr>
<td>Anus</td>
<td>1,687</td>
<td>1,540</td>
<td>1,400</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>9,312</td>
<td>6,700</td>
<td>5,700</td>
</tr>
<tr>
<td><strong>Total (Males)</strong></td>
<td><strong>12,002</strong></td>
<td><strong>8,800</strong></td>
<td><strong>7,550</strong></td>
</tr>
</tbody>
</table>
Two Licensed Prophylactic HPV Vaccines (L1 Virus-Like Particles)

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Merck</th>
<th>GlaxoSmithKline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trade name</td>
<td>Gardasil®</td>
<td>Cervarix™</td>
</tr>
<tr>
<td>HPV types</td>
<td>6, 11, 16, 18</td>
<td>16, 18</td>
</tr>
<tr>
<td>Adjuvant</td>
<td>AAHS</td>
<td>ASO4 Adjuvant (MPL + Alum)</td>
</tr>
<tr>
<td>Licensed</td>
<td>Female and males (ages 9-26yrs)</td>
<td>Females (ages 9-25yrs)</td>
</tr>
<tr>
<td>Expected coverage of protection</td>
<td>70% of Cervical Cancer, 90% Genital Warts</td>
<td>70% of Cervical Cancer</td>
</tr>
</tbody>
</table>

3 intra-muscular injections over 6 months
### Table 1
Proof-of-principle HPV VLP prophylactic efficacy trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Koutsky et al. (32)</th>
<th>Harper et al. (35)</th>
<th>Villa et al. (33)</th>
<th>Mao et al. (34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV VLP type</td>
<td>16</td>
<td>16, 18</td>
<td>6, 11, 16, 18</td>
<td>16</td>
</tr>
<tr>
<td>Adjuvant</td>
<td>Alum</td>
<td>AS04</td>
<td>Alum</td>
<td>Alum</td>
</tr>
<tr>
<td>Sponsor</td>
<td>Merck</td>
<td>GSK</td>
<td>Merck</td>
<td>Merck</td>
</tr>
<tr>
<td>Trial site</td>
<td>United States</td>
<td>United States,</td>
<td>United States,</td>
<td>United States</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Canada, Brazil</td>
<td>European Union,</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Brazil</td>
<td></td>
</tr>
<tr>
<td>Subject age</td>
<td>16–23</td>
<td>15–25</td>
<td>16–23</td>
<td>16–23</td>
</tr>
<tr>
<td>No. subjects (ATP)</td>
<td>1,533</td>
<td>721</td>
<td>468</td>
<td>1,505</td>
</tr>
<tr>
<td>Vaccination schedule (mo)</td>
<td>0, 2, 6</td>
<td>0, 1, 6</td>
<td>0, 2, 6</td>
<td>0, 2, 6</td>
</tr>
<tr>
<td>Follow-up (yr)</td>
<td>1.5</td>
<td>1.5</td>
<td>2.5</td>
<td>3.5</td>
</tr>
<tr>
<td>Persistent infectionsA</td>
<td>42/0 (100)</td>
<td>7/0 (100)</td>
<td>36/4B (90)</td>
<td>111/7C (94)</td>
</tr>
<tr>
<td>CIN1+D</td>
<td>9/0 (100)</td>
<td>6/0 (100)</td>
<td>3/0 (100)</td>
<td>24/0 (100)</td>
</tr>
</tbody>
</table>

Shown are according-to-protocol (ATP) analyses for the HPV types included in the vaccines. AValues are shown as number of controls versus number of vaccinees with persistent infections; values in parentheses indicate percent efficacy. BTen of 36 controls and 3 of 4 vaccinees were HPV DNA positive only at the last visit. CNineteen of 111 controls and 7 of 7 vaccinees were HPV DNA positive only at the last visit. DValues are shown as number of controls versus number of vaccinees that were CIN1+; values in parentheses indicate percent efficacy. GSK, GlaxoSmithKline.

Lowy DR, Schiller JT. JCI 2006; 116: 1167
Two Prophylactic HPV Vaccines: Protection Beyond Cervical Cancer

<table>
<thead>
<tr>
<th></th>
<th>Gardasil (Quadrivalent)</th>
<th>Cervarix (Bivalent)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cervix</strong></td>
<td>High protection against HPV-infection and related disease</td>
<td></td>
</tr>
<tr>
<td><strong>Vagina/Vulva</strong></td>
<td>Protection against HPV-infection and related disease</td>
<td>Not evaluated</td>
</tr>
<tr>
<td><strong>Penis</strong></td>
<td>Protection against HPV-infection</td>
<td>Not evaluated</td>
</tr>
<tr>
<td><strong>Anus</strong></td>
<td>Protection against HPV-infection and disease</td>
<td>Protection against HPV-infection</td>
</tr>
<tr>
<td><strong>Oropharynx</strong></td>
<td>Not evaluated</td>
<td>Protection against HPV-infection</td>
</tr>
</tbody>
</table>
Evolution of Recommendations for HPV Vaccination in the US

**Quadrivalent Vaccine**
Routine: females 11 or 12yrs* and 13-26 yrs if not previously vaccinated

**Quadrivalent or Bivalent**
Routine: females 11 or 12yrs* and 13-26 yrs if not previously vaccinated

**Quadrivalent**
Maybe given males 9-26yrs*

**Quadrivalent**
Routine: males 11 or 12yrs*
and 13-21 yrs if not previously vaccinated
May be given, 22-26 yrs

**WHO Advisory Group**
recommends a 2-dose schedule for girls, <15 years (0/6)

Year Changes:
- 2006: Quadrivalent Vaccine Routine
- 2007: Quadrivalent or Bivalent Routine
- 2008: Quadrivalent Routine
- 2009: Quadrivalent Routine
- 2010: Quadrivalent Routine
- 2011: Quadrivalent Routine
- 2012: Quadrivalent Routine
- 2013: Quadrivalent Routine
- 2014: Quadrivalent Routine
Potential Mechanisms of Vaccine-Induced Protection Against Infection and Disease

- **Humoral Immunity**: Neutralizing Antibodies
- **Cellular Immunity**: CTL, T helper
Cell-Mediated and Humoral Responses to HPV-16 L1 VLP vaccine

Immune Response to Vaccination:
- Type-specific neutralizing antibodies
- T-cell proliferation (CD4+ and CD8+ T cells)
- Complex cytokine responses (Th1, Th2 and inflammatory cytokines)
- Innate immune responses (DC activation)

(Pinto et al, JID 2003; García-Piñeres et al, EJI 2006; García-Piñeres et al, CVI 2007, Garcia-Pineres et al, JI 2009)
NCI Costa Rican Vaccine Efficacy Trial: Immunity Studies

- Optimization and validation of assays (serum and cervical secretions)
- Monitor antibody responses and duration of protection
- Understand immune mechanisms of protection and failure
  - Cross-protection
  - Immunogenicity of less than three doses

7,466 Women 18–25 years old

Hepatitis A Vaccine Havrix®

HPV-16/18 Vaccine Cervarix®

10 total years of follow-up
Validated Assays for Measurement of Antibodies in Serum and Cervix

HPV Serology Assays

- **Quantity:**
  - HPV IgG ELISA

- **Quality/Function:**
  - Pseudovirion neutralization assay
  - ELISA antibody avidity assay
  - Memory B cell ELISPOT

*All assays used in-house produced HPV VLPs, standards, and controls*
HPV-16/18 L1 VLP Vaccine Immunogenicity Study: Costa Rica Vaccine Trial

Antibody Levels (GMT) EU/mL

- HPV16
- HPV18

Months

Antibody Levels (GMT) EU/mL

- 0
- 1
- 6
- 7
- 12
- 18
- 24
- 30
- 36
- 42
- 48
Anti HPV-16 Antibody Over 5 Years Follow-Up (Quadrivalent vaccine)

Geometric Mean Antibody Titer (Log Scale)

Time Since Vaccination 1 (Months)

Vaccine
Natural infection

Olsson S et al. Vaccine 2007; 25:4931
Villa L et al. Vaccine 2006; 24: 5571
Durability of Antibody Response to 3 Doses of the Bivalent Vaccine: 9.4 yrs

Naud PS et al. Hum Vaccin Immunother 2014
Antibody Titers in Gardasil® and Cervarix® Recipients

* p<0.05, Mann-Whitney U test

Herrin et al. Hum Vaccin Immunother. In Press
Influence of Age at Vaccination in Females (HPV Quadrivalent Vaccine)

Levels of Antibodies in Serum Correlate Well with Levels in the Cervix

Kemp et al., *Vaccine*, 2008
## Cross-Protection Against Persistent Infection with Related High Risk HPV Types

**Cervarix HPV16/18 Vaccine**  
ATP analysis; >7,000 per arm: 3.5 yrs follow-up

<table>
<thead>
<tr>
<th>HPV Type</th>
<th># Vaccine</th>
<th># Placebo</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>31</td>
<td>21</td>
<td>102</td>
<td>79%</td>
</tr>
<tr>
<td>33</td>
<td>31</td>
<td>50</td>
<td>38%</td>
</tr>
<tr>
<td>45</td>
<td>10</td>
<td>27</td>
<td>76%</td>
</tr>
<tr>
<td>52</td>
<td>150</td>
<td>143</td>
<td>-5%</td>
</tr>
<tr>
<td>58</td>
<td>64</td>
<td>56</td>
<td>-15%</td>
</tr>
<tr>
<td>All of Above</td>
<td>255</td>
<td>336</td>
<td>24%</td>
</tr>
</tbody>
</table>

*Paavonen et al., Lancet 2009*
Protection Beyond Vaccine Types: HPV-16/18 L1 VLP Vaccine Induces Cross-Neutralizing Antibodies

Kemp et al., *Vaccine*, 2011
Kemp et al., *Vaccine*, 2012

*p<0.001*
HPV-16 Antibody Avidity Increases after Vaccination over 36 Months of Follow-up

Kemp et al., *Vaccine*, 2012
Dauner et al., *Mol Cell Probes*, 2012
<table>
<thead>
<tr>
<th># of Doses</th>
<th>Arm</th>
<th># of Women</th>
<th># of persistent HPV16/18 infections</th>
<th>HPV16/18 VE (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Control</td>
<td>3010</td>
<td>133</td>
<td>81% (71% to 88%)</td>
</tr>
<tr>
<td></td>
<td>HPV</td>
<td>2957</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Control</td>
<td>380</td>
<td>17</td>
<td>84% (50% to 96%)</td>
</tr>
<tr>
<td></td>
<td>HPV</td>
<td>422</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Control</td>
<td>188</td>
<td>10</td>
<td>100% (67% to 100%)</td>
</tr>
<tr>
<td></td>
<td>HPV</td>
<td>196</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Kreimer A.R. et al. *JNCI 2011*
HPV16 Antibody levels in Recipients of 1, 2 and 3 Doses of the bivalent HPV vaccine, Costa Rican Clinical Trial

Summary

• High efficacy for preventing HPV infection
• Generally safe and tolerable
• High levels of immunogenicity
  • >99% seroconversion rates in 9-26 years old
  • Antibody titers higher than in natural infection
  • Antibodies decline over time after the 3rd dose, but plateau by 18 months
  • Stable antibody levels up to 9 years of follow-up
  • Induction of T cell immunity and DC activation
• Non-inferiority of 2 doses, if given at 0, 6 month schedule
• The minimum protective antibody threshold not known

• **Current HPV vaccines will not eliminate the need for cervical cancer screening**
There are Still Many Unanswered Questions

Vaccine Performance
- Duration of protection/boosting requirements
- Alternative vaccination schedules/doses/adjuvant
- Immunogenicity and Efficacy in Males

Immunological Mechanisms of Protection/Failure
- Correlates of Protection/Effecter mechanisms (neutralizing antibodies)
- Determinants of long-term protection (B/T-cell memory)
- Epitopes
- Surrogates for evaluation of second generation vaccines
Acknowledgments

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PEG, Fundacion Inciensa, Costa Rica
  • Rolando Herrero
  • Ana Cecilia Rodriguez

For additional questions:
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Adolescent Vaccine (13-17 Years Old), United States, 2006-2012