HPV Vaccines: Efficacy Vs. Effectiveness, Next Generation Vaccines, and Controversies

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## HPV-Related Diseases in the US

<table>
<thead>
<tr>
<th>HPV-Related Disease</th>
<th>Estimated Number of Cases</th>
<th>Estimated Number (%) Related to HPV-6, -11, -16, or -18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical cancer</td>
<td>11,100</td>
<td>7,800 (~70%)</td>
</tr>
<tr>
<td>Anal cancer</td>
<td>4,650</td>
<td>3,260 (~70%)</td>
</tr>
<tr>
<td>Vulvar, vaginal, and penile cancers</td>
<td>6,900</td>
<td>2,070 (~30%)</td>
</tr>
<tr>
<td>Head and neck cancers</td>
<td>34,000</td>
<td>5,100 (~15%)</td>
</tr>
<tr>
<td>Recurrent respiratory papillomatosis</td>
<td>1,000</td>
<td>900 (~90%)</td>
</tr>
<tr>
<td>Precancerous cervical lesions (CIN2+)</td>
<td>500,000</td>
<td>200,000 (~40%)</td>
</tr>
<tr>
<td>Genital warts</td>
<td>500,000</td>
<td>425,000 (~85%)</td>
</tr>
</tbody>
</table>

Prophylactic HPV Vaccines

- Two vaccines based on L1 capsid (shell) protein of HPVs
- Bivalent HPV16/18, HPV2
  - Cervarix® GlaxoSmithKline
  - Regulatory approval in 50+ countries
  - US FDA approval likely based on expert committee approval in September of 2009
- Quadrivalent HPV6/11/16/18, HPV4
  - Gardasil® Merck
  - Regulatory approval in 100+ countries including the US
- Recommendations
  - Prioritize routine vaccination of females 9 to 15 years of age
Phase III Randomized Clinical Trials of HPV6/11/16/18 (Merck) or HPV16/18 (GSK) L1 VLP Vaccines in Susceptible Women (~16 to 25 Yrs)

<table>
<thead>
<tr>
<th>Merck Vaccine</th>
<th>vaccine placebo</th>
<th>vaccine efficacy (95% CI)</th>
<th>GlaxoSmithKline Vaccine</th>
<th>vaccine placebo</th>
<th>vaccine efficacy (96% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5865</td>
<td>5863</td>
<td>8040</td>
<td>8080</td>
<td></td>
</tr>
<tr>
<td>HPV 16/18- CIN2+</td>
<td>3</td>
<td>62</td>
<td>95% (85-99)</td>
<td>5</td>
<td>91</td>
</tr>
<tr>
<td>HPV6/11/16/18- Genital warts</td>
<td>3</td>
<td>67</td>
<td>96% (86-99)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Merck Vaccine: HPV6/11/16/18 L1 VLP with injections 0, 2, 6 mo. (3 years FU)  
GSK Vaccine: HPV16/18 L1 VLP with injections 0, 1, 6 mo. (3 year FU)
Additional RCT Findings

• Neither vaccine acts therapeutically to induce regression of established lesions

• Protection is HPV-type restricted
  – Both vaccines show partial protection against HPV-31

• Duration of protection is unknown although current evidence supports durability
  – Strong protection 6 to 8 years after VLP antibody levels have reached a plateau
  – The few vaccine failures not related to low antibody titers
  – Antigen challenge at 5 years stimulates an anamnestic response (characteristic of vaccine with long-lasting protection)
Prophylactic Efficacy Against HPV 6/11/16/18-Related Genital Lesions in Susceptible Men (15-27 years old)

Giuliano A. presented at EUROGIN, Nice France, November 2008

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>HPV6/11/16/18 Vaccine (n = 1,397)</th>
<th>Placebo (n = 1,408)</th>
<th>Vaccine Efficacy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genital Warts</td>
<td>3</td>
<td>28</td>
<td>89%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(66, 98)</td>
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Safety
U.S. Data for Monitoring Vaccine Safety after Licensure

- Vaccine Adverse Events Reporting System (VAERS)
  - Passive surveillance system
- Vaccine Safety Datalink (VSD)
  - Collaboration between CDC and 8 managed care organizations
  - Data from 8.8 million members captured annually (3% of US population)
  - Tests hypotheses based on pre- and post-licensure data
    - Rapid Cycle Analysis (RCA)
- Clinical Immunization Safety Assessment Network (CISA)
  - Clinical investigations of adverse event reports
  - Develop strategies to eliminate adverse events
- Vaccine Manufacturers – RCT and surveillance data
October 2008 U.S. Advisory Committee on Immunization Practices (ACIP) Meeting

• Post-vaccination syncope (fainting) happens with all adolescent vaccines, not just the HPV4 vaccine
• Available data do not support a causal relationship between HPV4 vaccine and death, Guillain-Barre Syndrome (GBS), Transverse Myelitis (TM), or venous thromboembolism
• No confirmed reports of anaphylaxis
• Pregnant women and those with reactions to vaccine components should not be vaccinated
• Surveillance and study of outcomes ongoing in VAERS, CISA, and VSD
• CDC and FDA continue to consider the HPV4 vaccine, Gardasil®, to be a safe and effective vaccine
Population-level Effectiveness
Population-level Effectiveness

- Coverage of US adolescent females is <40%
- Coverage in countries with school-based vaccination programs:
  - Scotland (12-18 yr old females) - 90%
  - England (12-13 yr old females) - 80%
  - Australia (12-18 yr old females) - 80%
- Preliminary efficacy data from Australian STD Clinic:
  - ~50% ↓ genital wart prevalence in young women, ~ 20% ↓ in young men, and no ↓ in young MSM
- Need for sentinel surveillance systems in the US
  - SEER for CIN2-3, AIS, cancer
  - VSD for CIN2-3, AIS, cancer, and genital warts
Next Generation Vaccines

- 9-valent HPV L1 VLP – Merck (results of efficacy VS HPV4 in ~August 2013)
- HPV L2 Vaccine (early development)
- HPV L1 recombinant Ty21a *Salmonella typhi* (early development)
- HPV L1 recombinant measles (early development)
Controversies
Challenges for Implementing HPV Vaccination Programs in the U.S.

- **Cost**
  - >$360 for the 3-dose series
  - >$300 for public health (Vaccine for Children program)

- **Consensus**
  - Poor understanding of HPV link with ano-genital cancers and warts
  - Selective presentations of the risk: benefit profile
  - Denial of adolescent sexual activity

- **Coverage**
  - Limitations of marketing and lobbying
  - 3 doses of the same vaccine
  - Importance of school-based immunization programs
# Vaccination Strategy Objectives

**Feudtner and Marcuse** *Pediatrics* 2001:107;1158

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<tr>
<th>Objectives</th>
<th>Mandatory</th>
<th>Recommended</th>
<th>Elective</th>
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<tbody>
<tr>
<td>Minimize deleterious disease consequences</td>
<td>Best</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimize deleterious vaccine consequences</td>
<td></td>
<td>Best</td>
<td></td>
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<tr>
<td>Maximize just distribution of benefits and burdens</td>
<td></td>
<td>Best</td>
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<tr>
<td>Optimize personal liberty to refuse or choose</td>
<td></td>
<td></td>
<td>Best</td>
</tr>
<tr>
<td>Promote family duty to protect child</td>
<td></td>
<td>Best</td>
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</tr>
<tr>
<td>Promote societal duty to protect children</td>
<td></td>
<td>Best</td>
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<tr>
<td>Use health care resources prudently</td>
<td></td>
<td>Best</td>
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