Demystifying the HPV vaccine: Is it really safe and effective?

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What is HPV?

- **Human Papillomavirus** – DNA virus with protein shell; infect skin and mucous membranes

- **How many people have genital HPV?**
  - >20 million people currently infected
  - 6.2 million new infections every year

- **Who gets genital HPV?**
  - Young people – rates decrease with increasing age
  - Associated with sexual behaviors – early onset, number of partners

- **Persistent infection with high risk HPV types**
  leads to cervical cancer
> 100 HPV Types

**Genital HPVs**
- sexual contact
- (>40 types)
  - **“High-risk” types**
    - 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58
  - low grade cervical abnormalities
  - genital pre-cancers
  - genital cancers
  - low grade cervical abnormalities
  - genital warts
  - respiratory papillomatosis

**Dermal HPVs**
- nonsexual contact
- (>50 types)
  - **“Common” warts**
    - (e.g., hands/feet)
    - 6, 11, 40, 42, 43, 44, 54, 61, 72, 73, 81

**“Low-risk” types**
- 6, 11, 40, 42, 43, 44
- 54, 61, 72, 73, 81
HPV Vaccine Structure

- Recombinant vaccine
- HPV L1 proteins self assemble into virus-like particles (VLP)
- L1 protein serves as antigen
- No live virus
- No thimerosal or mercury
## Licensed & Candidate Prophylactic HPV Vaccines

<table>
<thead>
<tr>
<th>Vaccine/Manufacturer</th>
<th>HPV Types</th>
<th>Doses</th>
<th>Adjuvant</th>
<th>Diseases Prevented</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quadrivalent Merck</td>
<td>6/11/16/18</td>
<td>0, 2, 6 months</td>
<td>Alum</td>
<td>Cervical Cancer, Genital Warts</td>
</tr>
<tr>
<td>Bivalent GlaxoSmithKline</td>
<td>16/18</td>
<td>0, 1, 6 months</td>
<td>Alum and MPL</td>
<td>Cervical Cancer</td>
</tr>
</tbody>
</table>
## Current Status of Prophylactic HPV Vaccines

<table>
<thead>
<tr>
<th>Vaccine/Manufacturer</th>
<th>FDA Application</th>
<th>FDA Status</th>
<th>US Licensure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quadrivalent Merck</td>
<td>Filed Dec 2005 Females 9-26 years and males 9-15 years</td>
<td>Approved for females 9-26 years</td>
<td>Approved June 8, 2006</td>
</tr>
<tr>
<td>Bivalent GlaxoSmithKline</td>
<td>Filed March 2007</td>
<td>Pending approval</td>
<td>Pending approval</td>
</tr>
</tbody>
</table>
Quadrivalent HPV Vaccine

- FDA approved June 8, 2006
- Noninfectious, recombinant, quadrivalent vaccine
- HPV types 6/11/16/18
- Approved for use in females 9-26 years of age
- Prevention of the following disease:
  - Cervical cancer
  - Cervical, vaginal and vulvar pre-cancer
  - Genital warts
Quadrivalent HPV Vaccine Clinical Development Program

- Efficacy studies in females 16-26 years
- Safety and immunogenicity studies in 9-15 year olds
- Clinical endpoints
  - Cervical cancer
    - Cervical pre-cancer/High grade cervical lesions
  - Vaginal and vulvar pre-cancers
  - External genital lesions/warts
Endpoints for Clinical Trials

0 to 1 Year

- Initial HPV Infection
  - Continuing Infection
    - Low grade disease
      - Cleared HPV Infection

0 to 3 Years

- Continuing Infection
  - Cervical Pre-cancer

Up to 20 Years

- Definitive Efficacy
  - Cervical Cancer
Endpoints for Clinical Trials

- 0 to 1 Year
- 0 to 3 Years
- Up to 20 Years

Initial HPV Infection → Continuing Infection → Low grade disease → Cleared HPV Infection

Definitive Efficacy

- Cervical Pre-cancer
- Cervical Cancer
Primary efficacy endpoint to show prevention of HPV16/18 - high grade disease and pre-cancer.
Quadrivalent HPV Vaccine

Efficacy Clinical Trials

- Total: 20,541 subjects
- 4 clinical trials
  - Protocol 005 – 2,391 women, 4 ½ years follow-up – HPV 16 component only
  - Protocol 007 – 551 women, 3 ½ years
  - FUTURE I (protocol 013) – 5,455 women, 3 years follow-up, 62 study sites in 16 countries
  - FUTURE II (protocol 015) – 12,167 women, 2 ½ years follow-up, 90 study sites in 13 countries
Clinical Trials Efficacy Analyses

- Per-protocol Efficacy
  - Was vaccine effective in reducing HPV 6/11/16/18 related disease in those who have not been exposed

- Intent-to-treat Efficacy
  - What was impact in reducing disease from HPV 6/11/16/18 in all subjects

- General Population Impact
  - What was impact in reducing all disease (regardless of HPV type) in all subjects
## Per-protocol Efficacy of Quadrivalent Vaccine

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Vaccine</th>
<th>Placebo</th>
<th>Efficacy</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Cases</td>
<td>N</td>
<td>Cases</td>
</tr>
<tr>
<td>HPV 16/18 related high grade disease and pre-cancer*</td>
<td>5305</td>
<td>1</td>
<td>5260</td>
<td>42</td>
</tr>
<tr>
<td>HPV 6/11/16/18 related genital warts and vaginal lesions**</td>
<td>2261</td>
<td>0</td>
<td>2279</td>
<td>60</td>
</tr>
</tbody>
</table>

## Intent-to-treat Efficacy of Quadrivalent Vaccine

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Vaccine</th>
<th>Placebo</th>
<th>% Reduced</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Cases</td>
<td>N</td>
<td>Cases</td>
</tr>
<tr>
<td>HPV 16/18 related high grade disease and pre-cancer*</td>
<td>6087</td>
<td>83</td>
<td>6080</td>
<td>148</td>
</tr>
<tr>
<td>HPV 6/11/16/18 related genital warts and vaginal lesions**</td>
<td>2723</td>
<td>28</td>
<td>2732</td>
<td>102</td>
</tr>
</tbody>
</table>

## General Population Impact of Quadrivalent Vaccine

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Vaccine</th>
<th>Placebo</th>
<th>% Reduced</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Cases</td>
<td>N</td>
<td>Cases</td>
</tr>
<tr>
<td>High grade disease and pre-cancer from any HPV type*</td>
<td>6087</td>
<td>219</td>
<td>6080</td>
<td>266</td>
</tr>
<tr>
<td>Genital warts and vaginal lesions from any HPV type**</td>
<td>2723</td>
<td>104</td>
<td>2732</td>
<td>157</td>
</tr>
</tbody>
</table>

Clinical Trials Efficacy Analyses

Summary

- Highly efficacious in those not previously exposed
- Significant impact on reducing disease related to vaccine HPV types
- Modest impact on overall disease reduction
- Full benefit of vaccine remains to be seen
Quadrivalent HPV Vaccine

Immunogenicity Data

- Duration of Immune Response
  - Followed levels of antibodies in 8,915 women and girls

- Bridging Efficacy to 9-15 year old girls
  - Clinical endpoints could not be measured in young girls
  - Antibody levels used as surrogate for efficacy in this age group
Immune Response to Quadrivalent Vaccine through 5 Years

**GMT** (Log Scale)

**Vaccination**

**Time Since Vaccination 1 (Months)**

- **HPV vaccine**
- **Placebo (Sero (+) and PCR (-) to HPV 16 at Day 1)**

*GMT = Geometric mean titer in mMU/mL (mMU = milli-Merck units).

Merck, unpublished data, Presented at ACIP meeting, June 2006
Bridging Efficacy of the Quadrivalent Vaccine to 9-15 year old girls

**Adolescent Girls**
9 to 15 years of age
N = 1,121

**Young Adult Women**
16 to 26 years of age
N = 4,229

*GMT = Geometric mean titer in mMU/mL (mMU = milli-Merck units).

Source: http://www.fda.gov/cber/label/hpvmer013007LB.pdf
## Local and Systemic Adverse Events

### Local Adverse Event

<table>
<thead>
<tr>
<th>Local Adverse Event</th>
<th>HPV Vaccine (n=5088)</th>
<th>Alum Placebo (n=3470)</th>
<th>Saline Placebo (n=320)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>83.9 %</td>
<td>75.4 %</td>
<td>48.6 %</td>
</tr>
<tr>
<td>Swelling</td>
<td>25.4 %</td>
<td>15.8 %</td>
<td>7.3 %</td>
</tr>
<tr>
<td>Erythema</td>
<td>24.6 %</td>
<td>18.4 %</td>
<td>12.1 %</td>
</tr>
<tr>
<td>Pruritus</td>
<td>3.1 %</td>
<td>2.8 %</td>
<td>0.6 %</td>
</tr>
</tbody>
</table>

### Systemic Adverse Event

<table>
<thead>
<tr>
<th>Systemic Adverse Event</th>
<th>HPV Vaccine (n=5088)</th>
<th>Placebo (n=3790)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>10.3 %</td>
<td>8.6 %</td>
</tr>
<tr>
<td>Nausea</td>
<td>4.2 %</td>
<td>4.1 %</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2.8 %</td>
<td>2.6 %</td>
</tr>
</tbody>
</table>

Source: http://www.fda.gov/cber/label/hpvmer013007LB.pdf
VAERS Data for Quadrivalent HPV Vaccine

- Vaccine Adverse Event Reporting System
- Updated data - Feb 2007
- 5 most frequently reported symptoms (total = 542)
  - Injection site pain 18%
  - Dizziness 11%
  - Syncope 11%
  - Fever 9%
  - Nausea 9%

Source: http://www.cdc.gov/nip/ACIP/slides/feb07/08-hpv-3-markowitz.pdf
Quadrivalent HPV Vaccine during Pregnancy and Lactation

- **Pregnancy**
  - Adverse events similar in vaccine and placebo groups
  - Currently not recommended
  - Further study required – Pregnancy Registry

- **Lactation**
  - No adverse events related to vaccine
  - Ok to get vaccine during lactation

Source: http://www.fda.gov/cber/label/hpvmer013007LB.pdf
Quadrivalent HPV Vaccine

Summary

- Highly efficacious in those not exposed
- Immune response sustained for 5 years
- Superior immune response in younger girls; no efficacy data
- Safe vaccine
Remaining Unanswered Questions

- Long term safety
- Extent of immunity
- Cross protection vs. type replacement
- Pre/post sexual debut
- Male vaccination
- Impact on cervical cancer deaths will not be apparent for long time
- Comparison to other HPV vaccines
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