No conflict of interest to disclose
Human Papillomavirus (HPV)

- Non enveloped double stranded DNA virus
- Genome of approximately 8 kb
- Spherical capsid 2 proteins L1 L2
- Early genes E1-E7
- Common in children
## More than 150 HPV types

<table>
<thead>
<tr>
<th>Skin lesions</th>
<th>Frequent</th>
<th>Less frequent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common, palmar, plantar, myrmecial, mosaic warts</td>
<td>1,2,27,57</td>
<td>4,29.41.60,63,65</td>
</tr>
<tr>
<td>Flat warts</td>
<td>3,10</td>
<td>28,29</td>
</tr>
<tr>
<td>Butcher’s warts</td>
<td>7</td>
<td>1,2,3,4,10,28</td>
</tr>
<tr>
<td>SCC Bowen’s disease</td>
<td>16</td>
<td>26,31,33,34,35,51,52,56,73</td>
</tr>
<tr>
<td>Epidermodysplasia verruciformis</td>
<td>3,5,8</td>
<td>9,12,14,15,17,19-25,36-38,47,49,50</td>
</tr>
<tr>
<td>Mucosal lesions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Condylomata acuminata</td>
<td>6,11</td>
<td>40,42-44,54,61,70,72,81</td>
</tr>
<tr>
<td>High grade intraepithelial neoplasias, invasive cancer</td>
<td>16</td>
<td>18,26,31,33,35,39,45,51-53</td>
</tr>
<tr>
<td>Buschke-Lowenstein</td>
<td>6,11</td>
<td>56,58,59,62,66,68,73,82</td>
</tr>
</tbody>
</table>
### Anogenital HPV

Approximately 40 HPV types infecting the genital area.

<table>
<thead>
<tr>
<th>Low risk types (6,11)</th>
<th>Benign or low-grade cervical cell changes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Genital warts</td>
</tr>
<tr>
<td></td>
<td>Respiratory papillomatosis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>High risk types (16,18)</th>
<th>Low-grade cervical cell abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High-grade cervical cell abnormalities: cancer precursor</td>
</tr>
<tr>
<td></td>
<td>Cancers: cervical, vulva, penis, anus, oropharynx</td>
</tr>
<tr>
<td></td>
<td>70% of cervical cancer caused by HPV 16,18</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>prevalence</th>
<th>In USA 80 million infected, 14 million new infections each year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>42% among female 14-59 y/o, 53% among female 20-24 y/o</td>
</tr>
</tbody>
</table>

CDC (MMWR) vol.63 No5 2014
New Cancers Probably Caused by HPV, USA 2006-2010

**Women (n = 17,600)**
- Cervix: 10,400 (59%)
- Oropharynx: 1,800 (10%)
- Vulva: 2,200 (13%)
- Anus: 2,600 (15%)
- Vagina: 600 (3%)
- Vulva: 2,200 (13%)

**Men (n = 9,300)**
- Oropharynx: 7,200 (77%)
- Anus: 1,400 (15%)
- Penis: 700 (8%)

CDC, United States Cancer Statistics (USCS), 2006-2010
HPV course of infection

Infects skin & mucous membrane keratinocytes

Variability of clinical appearance and course:

- Latent infection
- Subclinical infection
- Clinical infection
- Spontaneous resolution

Depends on interaction between

- HPV genotype,
- Viral genetic variables
- Host immune response
- Environment and life-styles
HPV replication
In matured keratinocytes in the suprabasal layers of the epithelium

Clinical HPV infection
Productive infection associated with benign neoplasm. All viral genes are expressed and the infection is transmissible

Clinical resolution

Activation

Clinical progression

Immune mediated viral clearance

HPV infection of a new host
Penetration to cells of the basal layer
Immune mediated viral clearance

Active HPV infection

Latent HPV infection
Viral gene expression is restricted to early genes that regulate only viral DNA transcription that cannot support a productive viral cycle. The infection is not transmissible

Subclinical HPV infection
Productive infection without clinical signs. All viral genes are expressed and the infection is transmissible

Immune mediated viral clearance

Management of Warts

No therapy

Too many treatment methods

- Destructive
- Virucidal
- Antiproliferative
- Immunological
- Complementary
When should we consider Immunotherapy

- Recalcitrant warts
- Recurrent warts
- Extensive warts
- Difficult location: periungual, palmoplantar
- Resolution without physical change or scaring
- Augmenting host response
- Treats all warts
**Immunotherapeutic modalities**

Stimulate or suppress the immune system

<table>
<thead>
<tr>
<th>Immune enhancement:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Systemic</td>
</tr>
<tr>
<td>• Topical</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Immunosuppressive:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Sirolimus</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Proinflammatory:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Interferons</td>
</tr>
<tr>
<td>• Interleukins</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cell mediated immunity inducers:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Candida, mumps antigens</td>
</tr>
<tr>
<td>• Topical contact sensitizers</td>
</tr>
</tbody>
</table>
Immunotherapy Diversity

**Topical**
- **Immune modifiers**
  - Imiquimod
  - Sinecatechines
- **Contact sensitizers**
  - DNCD, DPCP SADBE
- **Antigens**
  - BCG
  - PPD

**Intralesional**
- **Antigen Injection**
- **Extracted proteins**
  - PPD
- **Fungal**
  - Candida extract
  - Trichophyton
- **Viral**
  - Mumps
  - MMR
- **Bacterial**
  - BCG vaccine
  - Mycobacterium W
- **cytokines**
  - IFN, IL

**Systemic**
- **Immune enhancer**
  - Zinc
  - Cimetidine
  - Levamisole
  - Echinacea
  - Propolis
  - HPV vaccine
Imiquimod

Imiquimod

MyD88 Signaling Cascade

IFN-α, IL-12, IL-18

Antigen Presentation

NFκb

Naive T cell

Costimulatory Molecules

TH1

IFN-γ

TH2

IL-4, IL-5, IL-13

Immature Antigen-Presenting Cells

Mature Antigen-Presenting Cells

TLR7

Effecter Cytokines
## Imiquimod

**Approved for:**
- External genital, perianal warts
- Actinic keratosis
- Superficial BCC

**Reports of use in:**
- Plantar, periungual, subungual warts

**3 d/w for 16w, or 7d/w for 4w**

**Clearance:** 30-70%, low recurrence

**Alone or combined**

**Side effects:**
- Erythema, hypopigmentation
- Burning, pruritus
- Erosions, ulcerations, psoriasiform eruption
Sinecatechins

Extract of green tea leaves

8 different catechins:

- flavonoids responsible for the antioxidant effects of green tea

Action mode

- Indirect antioxidant activity
- Inhibitory effect on transcription factors NF-KB
- Inhibits enzymes increasing oxidative stress
  - Lipoxigenases
- Promoting apoptosis
- Immune stimulation effect by activating and induction
  - Lymphocytes, macrophages, langerhans
  - IL-1β, TNF-α, IFNγ
# Sinecatechins

<table>
<thead>
<tr>
<th>First FDA approved botanical drug for warts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Above 18 years of age</td>
</tr>
<tr>
<td>15% oint. 3/d for max 16W</td>
</tr>
<tr>
<td><strong>Not Recommended for</strong></td>
</tr>
<tr>
<td>• Immunocompromised, HIV</td>
</tr>
<tr>
<td>• genital herpes</td>
</tr>
<tr>
<td><strong>Adverse effects</strong></td>
</tr>
<tr>
<td>• Skin irritation in 67%, only 3% discontinue</td>
</tr>
<tr>
<td>• Burning, pain, itching, swelling</td>
</tr>
<tr>
<td><strong>Clearance</strong></td>
</tr>
<tr>
<td>• 54-65%</td>
</tr>
<tr>
<td><strong>Recurrence</strong></td>
</tr>
<tr>
<td>• 6-12%</td>
</tr>
</tbody>
</table>
Contact immunotherapy

Induce type IV hypersensitivity reaction

• Release of cytokines: IL-2, IFN
• Activating NK cells
• Lyses of virus infected cells

Diphencyperone – (DCP)
Diphenylcyclopropenone – (DPCP)
Squaric acid dibutylester – (SADBE)
Dinitrochlorobenzene – (DNCP) mutagenic
### Contact Immunotherapy

**Method:**
- Sensitization agent is applied to the skin
- Applied 1/W, for 3-6M
- Concentration augmented until desired inflammation

**Adverse effect:**
- Severe eczema
- Blistering
- Generalized eczema
- Contact urticaria
- Vitiligo
- Erythema multiforme-like

**Efficacy:**
- Complete cure: 70-90%
- Less painful than other modalities
- Less destructive
- Suitable for numerous and recalcitrant warts
Intralesional antigen Immunotherapy

Cell mediated immunity may control wart proliferation

- Wart proliferation and persistence in immunosuppressed
- Rapid appearance & spread of warts in transplant recipients
- Increase in CD4+ T cells in spontaneous wart regression
- Clearance of distant untreated warts after intralesional therapy

Antigenic stimulation of CMI can eradicate HPV

- Enhances immune system recognition of the virus
- Enables eradication of treated and untreated warts
- Induction of long term acquired immunity → Decreases in recurrence rates
Intralesional antigen Immunotherapy

potent host immune system

pre-sensitized Immune system

Th2 → Th1

Th1 cytokine profile:

• IL-1, IL-2, IL-12, IL-18 TNF-α IFN-γ
• TNF-α & IL-1 downregulate HPV gene transcription

Mononuclear cells proliferation promoting Th1 response

• Th1 cytokines activate cytotoxic T cells and NK cells
Intralesional antigen Immunotherapy

**Preliminary sensitization test**
- 0.1ml antigen injected intradermally
- Responders are enrolled

**Injection to the wart without test**
- Time, cost and compliance effective
- No correlation between sensitization and response
- Make sense when:
  - Antigens have common immune response like candida antigen
  - Antigens are part of immunization schedule like BCG, MMR

The largest wart is injected 0.1-0.3 ml

**Sessions:** 1-10

**Interval:** 1-4 weeks
What influences the response

- Vaccines containing different strains leading to different strain specific immunity.
- Different HPV types respond differently.
- Young patients respond better in some but not all studies.
- Common warts respond better in some studies.
- Shorter duration warts (< 6m) respond better than warts (>24m).
- Individual immune response to the antigen affects response.
- Combination therapy proves to be better than monotherapy.
## Intrallesional Antigen Immunotherapy

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Mode</th>
<th>WART</th>
<th>Complete response</th>
<th>recurrence</th>
<th>Side effect</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BCG</strong></td>
<td>Topical</td>
<td>Genital Common Plane</td>
<td>60-80%</td>
<td>Decreased</td>
<td>None</td>
<td>1/w 12</td>
</tr>
<tr>
<td></td>
<td>Injection 1. Lesion 2. arm</td>
<td>Common Plane Genital</td>
<td>40%</td>
<td>Decreased</td>
<td>Flu-like Pain Erythema induration</td>
<td>1/2w 1-10</td>
</tr>
<tr>
<td><strong>PPD</strong></td>
<td>Injection</td>
<td>Common Anogenital</td>
<td>30-76% Better in strong PPD test</td>
<td>Few</td>
<td>pain, fever, edema, eczema</td>
<td>1/1-3w 3-12</td>
</tr>
<tr>
<td><strong>Candida</strong></td>
<td>Injection First or biggest lesion</td>
<td>Common Untreated Resistant Recurrent</td>
<td>C.R 40-87% P.R 0 -41% Distal C.R 34-50%</td>
<td>Decreased</td>
<td>Pain, Bulla, Edema, Rare: myalgia fever, vitiligo</td>
<td>1/w 2-12 Mean 5</td>
</tr>
</tbody>
</table>
### Intralesional antigen Immunotherapy

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Mode</th>
<th>WART</th>
<th>Complete response</th>
<th>recurrence</th>
<th>Side effect</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mycobacterium w / indicus pranii vaccine</td>
<td>Injection I.L After sensitization</td>
<td>Common Genital</td>
<td>C.R 54-93%</td>
<td>None</td>
<td>Nodule, scar healed. Fever, pain, erosions, erythema</td>
<td>1/1-2-4w up to 12 Mean 4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Distal P.R 70-86%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMR Mumps Measles Rubella</td>
<td>I.L injection Without sensitization test mostly</td>
<td>Common</td>
<td>C.R 26-81% P.R 18-23%</td>
<td>5%</td>
<td>Pain, erythema, flu like,</td>
<td>1/2-3w Up to 6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Distal C.R 24-82%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Systemic Immunotherapy

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Mode</th>
<th>WART</th>
<th>Complete response</th>
<th>recurrence</th>
<th>Side effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Zinc oral</strong></td>
<td>10mg/kg/d up to 600mg/d 2m</td>
<td>Common Plane</td>
<td>C.R 50- 86%</td>
<td>N.A</td>
<td>Nausea, vomiting</td>
</tr>
<tr>
<td><strong>Zinc topical</strong></td>
<td>5%, 10%, 20% 3/d 4w, 3m</td>
<td>Common</td>
<td>C.R 5- 50%</td>
<td>N.A</td>
<td>Irritation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Plane</td>
<td>C.R 42-85%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cimetidine</strong></td>
<td>20-40mg/kg 3m</td>
<td>Common Plane Genital</td>
<td>C.R 24 – 87%</td>
<td>Decreased</td>
<td>GI complains</td>
</tr>
<tr>
<td><strong>Levamisole</strong></td>
<td>150mg/d 3d/14d - 5mg/kg/2w 5m</td>
<td>Common</td>
<td>Similar to placebo</td>
<td>N.A</td>
<td>Rash, nausea, cramps, flu-like, alopecia</td>
</tr>
</tbody>
</table>
Virus-like particle (VLP) vaccines

- The L1 major capsid protein expressed using recombinant technology

- L1 proteins self-assemble into VLPs

- L1 protein is type specific, some structural analogies

- Non infectious
# Available HPV vaccines

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Abbrev</th>
<th>HPV Types Protected Against</th>
<th>Which Cause</th>
<th>Licensed For</th>
<th>Dose Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gardasil</td>
<td>Quadrivalent 4vHPV</td>
<td>6, 11, 16, &amp; 18</td>
<td>Most HPV-related cancers and genital warts</td>
<td>Males &amp; Females:</td>
<td>3 dose series:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>9-26 years</td>
<td>0, 2, 6 months</td>
</tr>
<tr>
<td>Gardasil 9</td>
<td>9-valent 9vHPV</td>
<td>6, 11, 16, 18, 31, 33, 45, 52, &amp; 58</td>
<td></td>
<td>Females:</td>
<td>3 dose series:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10-25 years</td>
<td>0, 1, 6 months</td>
</tr>
<tr>
<td>Cervarix®</td>
<td>Bivalent 2vHPV</td>
<td>16 &amp; 18</td>
<td>Most HPV-related cervical, anal, &amp; throat cancer</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Genital warts

These HPV Types Cause:

- Genital warts
- ~66% of Cervical Cancers
- ~15% of Cervical Cancers

HPV Types Included in Vaccine

<table>
<thead>
<tr>
<th></th>
<th>6</th>
<th>11</th>
<th>16</th>
<th>18</th>
<th>31</th>
<th>33</th>
<th>45</th>
<th>52</th>
<th>58</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bivalent</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quadrivalent</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9-valent</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Efficacy - HPV4 (Gardasil)

- 98% efficacy preventing cervical pre-cancers in previously uninfected women
- Nearly 100% efficacious preventing vulvar/vaginal pre-cancers and genital warts
- 98% efficacy against HPV 6,11 related genital warts in women
- 89% efficacy for prevention of persistent HPV 6,11, 16, 18 infection
- In women previously exposed to HPV protects against reinfection or reactivation
- Not effective against progression to disease or clearance of infection in DNA detected HPV
- May offer cross-protection against HPV type 31, 33, 45, 52, 58
- 89% efficacy against HPV 6,11, 16,18 related genital warts in men
- 74% efficacy against HPV 6,11 related AIN in MSM

MMWR / August 29, 2014 / vol. 63/No.5
Efficacy - HPV2 (Cervarix)

- Efficacy 96-98% in prevention of cervical pre-cancers
- 94% and 91% efficacy for prevention of persistent HPV 16, 18 infection respectively
- Not effective against progression to disease or clearance of infection in DNA detected HPV
- Not effective in preventing genital warts
- Appears to offer cross-protection against other HPV sub-types (31, 45, 52)

MMWR / August 29, 2014 / vol. 63/No.5
Cervarix induces higher antibody titers against HPV 16 and 18 than Gardasil

Both vaccines appear to offer cross-protection against other HPV types, but Cervarix may offer more

Gardasil offers protection against genital warts (HPV 6,11)

Gardasil demonstrated vulvar/vaginal cancer protection

Gardasil approved for use in males

Einstein et al, *Hum Vaccines* 2009
Bonnanni et al, *Vaccine* 2009
Medeiros et al, *Int J Gynecol Cancer* 2009
9-valent HPV vaccine trials

Efficacy

• ~97% protection against HPV 31,33,45,52,58-related outcomes
• Similar protection against HPV 6,11,16,18-related disease

Non-inferior immunogenicity

• For HPV 6,11,16,18 compared with 4vHPV in 16–26 and 9–15 year olds
• For all 9 HPV vaccine types in adolescent females and males compared to adult females and in adult males compared to adult females

9-valent HPV vaccine safety

- Trials included >15,000 9vHPV vaccines

- Generally well tolerated; safety profile similar to 4vHPV

  - 9vHPV - more injection-site reactions
    - swelling (40.3% vs 29.1%)
    - erythema (34.0% vs 25.8%)

- Injection-site erythema and swelling increased with number of doses
ACIP recommendations

- Routine vaccination at age 11 or 12 years (can be started at 9 years of age).
- Vaccination recommended through age 26 for females and through age 21 for males not previously vaccinated.
- Vaccination recommended for men who have sex with men and immunocompromised men through age 26.
- Vaccination of females is recommended with 2vHPV, 4vHPV or 9vHPV.
- Vaccination of males is recommended with 4vHPV or 9vHPV.
Recommendations: National Organizations

- Vaccine most effective if given before 1st sexual contact
- Females who have abnormal Pap tests, positive HPV tests, or genital warts can receive HPV vaccine
- Data do not indicate vaccine therapeutic effect on existing HPV infection, cervical lesions, or genital warts
- Vaccination can provide protection against infection with vaccine HPV types not already acquired
- Minimal interval between injection:
  - 1 and 2 is 4 weeks
  - 2 and 3 is 12 weeks
  - 1 and 3 is 24 weeks
Local adverse reactions
in females and males aged 9–26 years, within 5 days of quadrivalent HPV vaccination

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Quadrivalent vaccine %</th>
<th>AAHS control %</th>
<th>Saline control %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Females</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 5,088</td>
<td></td>
<td>N = 3,470</td>
<td>N = 320</td>
</tr>
<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>24.7</td>
<td>18.4</td>
<td>12.1</td>
</tr>
<tr>
<td><strong>Males</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 3,093</td>
<td></td>
<td>N = 2,029</td>
<td>N = 274</td>
</tr>
<tr>
<td>Pain</td>
<td>61.4</td>
<td>50.8</td>
<td>41.6</td>
</tr>
<tr>
<td>Swelling</td>
<td>13.9</td>
<td>9.6</td>
<td>8.2</td>
</tr>
<tr>
<td>Erythema</td>
<td>16.7</td>
<td>14.1</td>
<td>14.5</td>
</tr>
</tbody>
</table>

http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM111263
Local and general adverse reactions in females aged 9–25 years, within 7 days of bivalent HPV vaccination

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Bivalent HPV vaccine (9–25 yrs) %</th>
<th>Hepatitis A (15–25 yrs) %</th>
<th>Hepatitis A (10–14 yrs) %</th>
<th>Al(OH)₃ control (15–25 yrs) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local</td>
<td>N = 6,669</td>
<td>N = 3,079</td>
<td>N = 1,027</td>
<td>N = 549</td>
</tr>
<tr>
<td>Pain</td>
<td>91.9</td>
<td>78.0</td>
<td>64.2</td>
<td>87.2</td>
</tr>
<tr>
<td>Redness</td>
<td>48.4</td>
<td>27.6</td>
<td>25.2</td>
<td>24.4</td>
</tr>
<tr>
<td>Swelling</td>
<td>44.3</td>
<td>19.8</td>
<td>17.3</td>
<td>21.3</td>
</tr>
<tr>
<td>General</td>
<td>N = 6,670</td>
<td>N = 3,079</td>
<td>N = 1,027</td>
<td>N = 549</td>
</tr>
<tr>
<td>Fatigue</td>
<td>54.6</td>
<td>53.7</td>
<td>42.3</td>
<td>53.6</td>
</tr>
<tr>
<td>Headache</td>
<td>53.4</td>
<td>51.3</td>
<td>45.2</td>
<td>61.4</td>
</tr>
<tr>
<td>GI</td>
<td>27.9</td>
<td>27.3</td>
<td>24.6</td>
<td>32.8</td>
</tr>
<tr>
<td>Fever (≥99.5°F)</td>
<td>12.9</td>
<td>10.9</td>
<td>16.0</td>
<td>13.5</td>
</tr>
<tr>
<td>Rash</td>
<td>9.5</td>
<td>8.4</td>
<td>6.7</td>
<td>10.0</td>
</tr>
<tr>
<td>Myalgia</td>
<td>48.8</td>
<td>44.9</td>
<td>33.1</td>
<td>—</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>20.7</td>
<td>17.9</td>
<td>19.9</td>
<td>—</td>
</tr>
<tr>
<td>Urticaria</td>
<td>7.2</td>
<td>7.9</td>
<td>5.4</td>
<td>—</td>
</tr>
</tbody>
</table>

http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM186981
VAERS (Vaccine Adverse Events Reporting System) associated with HPV4, 2006-2014

25,063 reports

- **92% considered not serious**
  - Most common – local reaction/soreness at injection site
  - Included fainting, headache, nausea, fever
  - Falls after fainting potentially serious

- **8% considered serious adverse events**
  - Guillain Barre, autoimmune disorders (many reports not verified, incidence not greater than background rate)
  - Blood clots – 90% in girls with other risk factors (birth control pills, smoking, obesity)
  - Deaths (96 reported, 47 confirmed – most with other causes)

cdc.gov/vaccinesafety
Thank you