DISCLOSURE:
Dr. Humiston's institution (CMH) receives funding from "Pfizer Independent Grants for Learning & Change" for her work to develop and test a curriculum to teach residents about how to manage vaccine hesitancy. This relationship is not relevant to this presentation.

Dr. Humiston's presentation today was funded by a grant from CDC to APA.
Vaccination Coverage, Teens Ages 13-17 years, U.S.

Markowitz et al., Academic Pediatrics 2018 18, S3-S10 DOI:

HPV vaccine

MO 51.6%

Tdap

MO 83.9%

Up-to-date HPV Vaccination Rates, 2016

Legend:

22.6 - 25.8

35.9 - 41.6

41.9 - 45.6

45.7 - 51.1

51.2 - 70.8

NA
"Here’s the bottom line: nothing goes further than having a deep knowledge of the issues, a sincere, meaningful and trustworthy connection with the family, and a strongly held personal conviction that vaccines save lives and prevent misery."

The Vaccine Handbook

---

**Topic #2**

HPV disease causes loss of lives and plenty of misery.

HPV vaccine prevents this.

[https://www.cdc.gov/hpv/hcp/more-than-screening/infographic.html](https://www.cdc.gov/hpv/hcp/more-than-screening/infographic.html)

---

**Human Papillomavirus**

- A virus that infects human skin and mucosal surfaces
- Transmitted easily
  - >90% of men and
  - >80% of women will be infected with ≥2 type of genital HPV at some time
- Some strains cause cancers
HPV Types Differ in Their Disease Associations

- ~40 Types
- Mucosal sites of infection
- Cutaneous sites of infection
- ~80 Types
- Common Hand and Foot Warts

~40 Types
- Low risk (non-oncogenic)
- HPV 6, 11 most common

~80 Types
- Genital Warts
- Laryngeal Papillomas
- Low-Grade Cervical Disease

Laryngeal Papillomatosis

- Annual cases per 100,000: ~4 children, 1.8 adults
- Benign tumors along the aerodigestive tract
- Caused by HPV infection of the throat
- Lead to narrowing of the airway
- Treatment
  - Aims to remove the papillomas and limit their recurrence
  - Repeated treatments usually are needed
  - Primarily treated surgically (laser microsurgery)
- Though total recovery may be observed, it is often persistent despite treatment
Incident cases of juvenile onset recurrent respiratory papillomatosis notified in Australia per year 2012–2016

Among incident cases no mothers were vaccinated pre-pregnancy

Australia has had extensive 4-valent HPV vaccination program (females 12–26 years old, started in 2007)

Genital warts

- > 3 million US cases per year
- Highly transmissible
  - May be transmitted during birth
  - Autoinoculation
  - Non-penetrative sexual activity
  - Penetrative sex
- Treatment can help, but there is no cure

Near-disappearance of genital warts in Australia following introduction of HPV vaccination

70% 4-valent HPV vaccination rate for females 12-26 only, started in 2007

Australia has had extensive 4-valent HPV vaccination program (females 12–26 years old, started in 2007)

©2013 by British Medical Journal Publishing Group
HPV Types Differ in Their Disease Associations

- 40 Types
  - Mucosal sites of infection
  - Low-risk (non-oncogenic) HPV 6, 11 most common
- 80 Types
  - Cutaneous sites of infection
  - High-risk (oncogenic) HPV 16, 18 most common

Cancers Caused by HPV per Year, U.S., 2010–2014

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>Percentage probably caused by any HPV type</th>
<th>Number probably caused by any HPV type</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>Cervix</td>
<td>91%</td>
<td>10,600</td>
</tr>
<tr>
<td>Vagina</td>
<td>75%</td>
<td>600</td>
</tr>
<tr>
<td>Vulva</td>
<td>67%</td>
<td>2,600</td>
</tr>
<tr>
<td>Penis</td>
<td>63%</td>
<td>0</td>
</tr>
<tr>
<td>Anus*</td>
<td>91%</td>
<td>3,800</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>70%</td>
<td>2,100</td>
</tr>
<tr>
<td>TOTAL</td>
<td></td>
<td>19,700</td>
</tr>
</tbody>
</table>

*Includes anal and rectal squamous cell carcinomas

Sources: [HPV vaccination and prevention](https://www.cdc.gov/hpv/prevention.html) and Saraiya M et al. J Natl Cancer Inst 2015;107:djv086

% of HPV types found in common HPV related cancers, US

9-valent vaccine is estimated to prevent:
- 85% of cervical
- 70% of oropharyngeal
- 80% of anal
- 60% of penile cancers
Do women still actually get cervical cancer & does anyone die of it?

Isn’t early detection enough?

(Do we really need to prevent infection?)

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HPV-Associated Cervical Cancer Incidence Rates, 2014


---

Cervical Cancer During Child-bearing Years

38% of cervical cancers occur in women between the ages of 20 & 44 years.

Cervical Dysplasia

- **Mild dysplasia (CIN1)**
  - aka Low-grade Squamous Intraepithelial Lesion (LSIL)
  - Regression is the norm
  - 1.4 million/year in U.S.
  - Conservative follow-up

- **Moderate/severe dysplasia (CIN2/3)**
  - aka High-grade Squamous Intraepithelial Lesion (HSIL)
  - High risk for progression to cancer
  - 339,000/year in U.S.
  - LEEP offers high cure rate

Loop electrosurgical excision procedure (LEEP) or a cold-knife cone biopsy is used to treat high grade cervical dysplasia and even early cervical cancer.
Even pre-cancerous lesions have implications for a woman & her offspring because LEEP is associated with:
- Perinatal mortality
- Preterm delivery
- Low birth weight
- Long term developmental outcomes
- Neonatal intensive care costs

We need HPV vaccination to eliminate first peak of HPV acquisition

Within 8 years of U.S. vaccine introduction 4vHPV-type prevalence has decreased significantly

Vaccine effectiveness: 83%

Compared to 2003-2006, 4vHPV prevalence in sexually active 14- to 24-year-olds in 2011-2014 decreased
- 89% among those vaccinated
- 34% among those unvaccinated which suggests herd protection
Trends in high-grade cervical abnormalities (histologically-confirmed) by age, 2000-2015, as recorded on the VCCR, Australia

From the Victorian Cervical Cytology Report, 2015

Vaccination protects against invasive HPV-associated cancers
Data from the Finnish Cancer Registry, Helsinki, Finland

<table>
<thead>
<tr>
<th>MALIGNANCIES</th>
<th>Vaccinated Women</th>
<th>Unvaccinated Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervix</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Vulva</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Oropharyngeal</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Vaginal, anal</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>All HPV assoc CA</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Breast</td>
<td>2</td>
<td>3.0</td>
</tr>
<tr>
<td>Thyroid</td>
<td>1</td>
<td>3.5</td>
</tr>
<tr>
<td>Melanoma</td>
<td>3</td>
<td>4.6</td>
</tr>
<tr>
<td>Other skin</td>
<td>2</td>
<td>3.0</td>
</tr>
</tbody>
</table>


4vHPV efficacy trial in women 26–29 years
Interim 10 year follow-up (14 years planned)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>N cases/ person-years at risk</th>
<th>Incidence /100 person-years at risk</th>
<th>HPV 6/11/16/18-related CIN and vulvar/vaginal cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV E6/11/16/18-related CIN</td>
<td>2449</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Time since day:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–4 years</td>
<td>0/1990</td>
<td>864 (0.4)</td>
<td></td>
</tr>
<tr>
<td>4–6 years</td>
<td>0/2568</td>
<td>4.297 (0.1)</td>
<td></td>
</tr>
<tr>
<td>6–8 years</td>
<td>0/2033</td>
<td>3.429 (0.1)</td>
<td></td>
</tr>
<tr>
<td>8–10 years</td>
<td>0/1449</td>
<td>2.866 (0.1)</td>
<td></td>
</tr>
</tbody>
</table>

1 case of CIN1 with HPV types 16, 45, 52 concurrently detected

4v HPV immunogenicity trial in adolescents 9–15 years
Final 10 year follow-up

- No cases of HPV 6,11,16,18 disease
- 10 persistent infections >6 months, 2 > 12 months
- This is a 90% reduction compared with placebo groups from older trials (No placebo group for this trial as considered unethical to withhold vaccine)

<table>
<thead>
<tr>
<th>Gender</th>
<th>Cases/100 person-years 10 year follow up 9-15 year olds</th>
<th>Cases/100 person-years 1-4 year follow up of 16-16 year olds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>0.4-0.6</td>
<td>6</td>
</tr>
<tr>
<td>Females</td>
<td>0.3</td>
<td>4</td>
</tr>
</tbody>
</table>

Das and Saah Eurogin 2016

Without vaccination, annual burden of genital HPV-associated disease in U.S. females

- >4,000 cervical cancer deaths
- >12,000 new cases of cervical cancer
- 330,000 new cases of HSIL: CIN2/3 (high grade cervical intraepithelial neoplasia)
- 350,000 new cases of genital warts
- 1.4 million new cases of LSIL

Data Sources: American Cancer Society. 2008; Schiffman, Mark, and Philip E. Castle. ; Koshiol Sex Transm Dis. 2004; Insinga, Ralph P., Erik J. Dasbach, and Elamin H. Elbasha. 2005

Extrapolating the prior pyramid with projections of vaccine efficacy based on Australian data

Cervical cancer

- 46% reduction in CIN2/3 requiring LEEP
- 75% if vaccination by age 14
- 92% reduction in genital warts
- 35% reduction in CIN1

Data Sources: Gertig, 2013; Read, 2013; Smith, 2015
Beyond the Statistics: What HPV Means to Women's Lives

Rebecca Perkins and Tamika Felder

http://www.academicpediatrics.net/article/S1876-2859(17)30169-9/fulltext

Obviously, we want to prevent HPV infection in females.

Why do we want to protect males from HPV?

Why vaccinate males?

- Non-oncogenic problems
- Prevent HPV infection of females
- Male only: Penile cancer
- Both sexes:
  - Anal cancer
  - Oropharyngeal cancer
Oropharyngeal Cancer

- 11,000 cases annually, 9,000 in men
- Rise in incidence and changing patient demographics due to HPV
- Now more common than cervical cancer
- No screening test
- Good survival statistics

Photo Credit: Dr. Michael Moore

Side effects of non-surgical therapy

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Percent affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taste Disturbance</td>
<td>88%</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>36%</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>29-38%</td>
</tr>
<tr>
<td>Esophageal Stricture</td>
<td>5%</td>
</tr>
<tr>
<td>Require G tube &gt; 1 year</td>
<td>9%</td>
</tr>
</tbody>
</table>

Photo credit: www.jpalliativecare.com
Incidence of Diseases covered in Adolescent Vaccine Series

Deaths from Diseases covered in Adolescent Vaccine Series

Annual Costs of HPV-associated Diseases, US

<table>
<thead>
<tr>
<th>HPV-Associated Problem</th>
<th>U.S. Cost*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genital warts treatment</td>
<td>$2.88 Million</td>
</tr>
<tr>
<td>Cervical cancer screening and follow-up of abnormal tests</td>
<td>$6.6 Billion</td>
</tr>
<tr>
<td>All HPV-associated diseases, including cancer</td>
<td>$8 Billion</td>
</tr>
</tbody>
</table>

*Based on 2010 dollars
HPV prevention is easier than ever.

**Dosing recommendations**

- **Dose 1**
- **Dose 2** 6-12 mos after dose 1
- **Dose 3** 6-12 mos after dose 2

- Started series before 15th birthday: needs 2 doses
- Started series on or after 15th birthday: needs 3 doses

**What forms of “immunocompromise” necessitate a 3-dose HPV vaccine series?**

<table>
<thead>
<tr>
<th>Needs 3 doses irrespective of age:</th>
<th>Can use 2 dose series for those initiating before 15th birthday:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary or secondary conditions that might reduce cell-mediated or humoral immunity</td>
<td>- Asthma</td>
</tr>
<tr>
<td>Examples:</td>
<td>- Asplenia</td>
</tr>
<tr>
<td>B lymphocyte Ab deficiencies</td>
<td>- Diabetes mellitus</td>
</tr>
<tr>
<td>T lymphocyte complete or partial defects</td>
<td>- Sickle cell disease</td>
</tr>
<tr>
<td>HIV infections</td>
<td>- Chronic granulomatous disease</td>
</tr>
<tr>
<td>Malignant neoplasm</td>
<td>- Chronic disease of liver, lung, kidneys</td>
</tr>
<tr>
<td>Transplantation</td>
<td>- Heart disease</td>
</tr>
<tr>
<td>Autoimmune disease</td>
<td>- CNS barrier defects (eg, cochlear implant)</td>
</tr>
<tr>
<td>Immunosuppressive therapy</td>
<td>- Complement deficiency, persistent complement component deficiency</td>
</tr>
</tbody>
</table>

- Asthma
- Asplenia
- Diabetes mellitus
- Sickle cell disease
- Chronic granulomatous disease
- Chronic disease of liver, lung, kidneys
- Heart disease
- CNS barrier defects (eg, cochlear implant)
- Complement deficiency, persistent complement component deficiency
Memory B cells require at least 4-6 months to mature and differentiate into high-affinity B cells. A 6-month interval between first and last dose allows the last dose to efficiently reactivate memory B cells.

### Case example - 1

A boy is starting the HPV vaccine series on his 15th birthday. **How many doses does he need in total?**

- A. 0
- B. 2
- C. 3

This adolescent needs 3 doses (0, 1-2, 6 months schedule) because he is starting the series on (or after) the 15th birthday.

### Case example - 2

A 13-year-old has a history of 2 doses of HPV vaccine: 4vHPV given at age 12 years and 9vHPV given 6 months later. **How many more doses are needed?**

- A. 0
- B. 1
- C. 2

No further doses are recommended because she initiated vaccination before the 15th birthday and received 2 doses of vaccine 6 months apart.
Case example - 3
A 13 year old has a history of 2 doses of HPV vaccine:
4vHPV given at age 11 years & 9vHPV given 2 months later.
How many more doses are needed?
A. 0 
B. 1
C. 2

1 more dose. Although she initiated the vaccination series before her 15th birthday, she needs another dose because HPV vaccine doses #1 and #2 were administered <5 months apart.
Give a 3rd dose with a minimum of 12 weeks between doses 2-3 and a minimum of 5 months between doses 1-3.

Case example - 4
A (spunky) 16 year old had 1 dose of HPV vaccine:
4vHPV given at age 11 years
How many more doses are needed?
A. 0 
B. 1
C. 2

1 more dose...Her first dose was before her 15th birthday.
Complete her series today.

Topic #4
What are the HPV vaccine true contraindications and precautions?
Which of the following is a **contraindication** to HPV vaccine?

A. Pregnancy
B. Moderate or severe acute illness with or without fever
C. A severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component
D. All of the above
E. B and C

https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/contraindications.html

Which of the following is **contraindication** to HPV vaccine?

A. Pregnancy (precaution)
B. Moderate or severe acute illness with or without fever (precaution)
C. A severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component

https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/contraindications.html

None of these is a contraindication

**COMMONLY MISUNDERSTOOD**
- Lack of previous physical examination
- Current antibiotic use
- History of HPV
- Autoimmune disease

**ILLNESS**
- Mild acute illness, with or without fever
- Mild respiratory illness (including most cases of otitis media)
- Mild gastroenteritis
- Convalescent phase of illness
- Exposure to an infectious disease

**REACTION TO PREVIOUS VACCINATION**
- Low-grade or moderate fever and/or local reaction after a previous dose
- Fainting (syncope) after a previous dose
Topic 5: Deep knowledge of FAQs

1. Why give it so young?
2. Should we give it to 9 year olds?
3. Should I only give it to kids at “high risk?”
4. Will it cause infertility?
5. Is it safe?

Higher effectiveness with vaccination at younger ages

% Reduction in cervical dysplasia 5 years after vaccination, by age at vaccination

Gertig DM, BMC Med 2013
Antibody response at age 9-13 vs. 16-26 years

Follow-up through month 36
- 2 doses (0, 6 months) in 9-13 yr olds (black)
- 3 doses (0, 1, 6 months) in 16-26 yr olds (red)
- 3 doses (0, 1, 6 months) in 16-26 yr olds (green)

Antibody kinetics similar in 3 groups


Slide presented by Dr. L. Markowitz, 10/2016

Will immunity last? Follow-up through month 60

Results: Antibody kinetics
- Similar in 3 groups
- Steady
- Natural infection

Source: Romanowski, Hum Vaccine 2016
When should the bike helmet go on?

A. Before they get on their bike
B. When they are riding their bike in the street
C. When they see the car heading directly at them
D. After the car hits them

Topic 5: Deep knowledge of FAQs

1. Why give it so young?
2. Should we give it to 9 year olds?
3. Should I only give it to kids at “high risk?”
4. Will it cause infertility?
5. Is it safe?
Topic 5: Deep knowledge of FAQs

1. Why give it so young?
2. Should we give it to 9 year olds?
3. Should I only give it to kids at “high risk?”
4. Will it cause infertility?
5. Is it safe?

The effect of HPV vaccination on fecundability (the ability to get pregnant)

HPV vaccination:

- Had no effect on fecundability overall
- Was positively associated with fecundability among women with a history of STI

Do we have enough data to KNOW that the vaccine is safe?
HPV vaccine long-term safety data

No increased risk of:

- 2011 - allergic reactions, anaphylaxis, Guillain–Barré Syndrome, stroke, blood clots, appendicitis, or seizures (than unvaccinated or who received other vaccines)
- 2013 - (almost 1 million girls) blood clots or AEs related to the immune & CNS
- 2014 - (>1 million women) venous thromboembolism or blood clots
- 2012 and 2014 - (2 studies) autoimmune disorders
- 2015 - Multiple sclerosis or other demyelinating diseases
- 2016 - over 60 conditions

2012 - vaccine may be associated with skin infections where the shot is given during the 2 weeks after vaccination and fainting on the day the shot is received

See, HV&A, 2016; Cameron Int Med Journal

9vHPV Vaccine Safety

- 7 pre-licensure studies including 15,000 males and females
- Generally well tolerated
  - Adverse event profile similar to that of 4vHPV across age, gender, race, and ethnicity
  - More injection-site reactions expected among those who receive 9vHPV

More HPV Vaccine Safety FAQ

- Can HPV vaccines damage women's ovaries?
  No evidence that HPV vaccination causes reproductive problems in women, including premature ovarian failure

- Can HPV vaccines cause Postural Orthostatic Tachycardia Syndrome (POTS)?
  - There are no unusual or unexpected patterns detected among these cases of POTS following Gardasil vaccination
  - CDC monitoring through VAERS has not detected any safety concern of POTS following HPV vaccination

HPV is very common and causes bad disease

HPV vaccine is effective, long-lasting, and safe

You and your office team can prevent cancer by vaccinating all everyone!