What will society gain from HPV vaccination—and how can we get there faster?

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Presenter Disclosure Information

• I, Rebecca Perkins, have been asked to disclose any significant relationships with commercial entities that are either providing financial support for this program or whose products or services are mentioned during our presentations.
  • I have no relationships to disclose.

• I may/will discuss the use of vaccines in a manner not approved by the U.S. Food and Drug Administration.
  • But in accordance with ACIP recommendations.
Objectives

• Latest understanding of HPV disease
• Effectiveness and Safety of HPV vaccination
• Strategies for effective communication
• Implications of possible age expansion
• Activities of MA HPV coalition
Every year in the US 43,000 people are diagnosed with a cancer caused by HPV.
43,000 new cancers probably caused by HPV each year

*Includes anal and rectal squamous cell carcinomas

Oropharyngeal Cancer: a new epidemic

- 18,000 cases annually, 15,000 in men
- More common than cervical cancer
- HPV-related cancers increased by 225% in the past 20 years
- Rise in incidence and changing patient demographics due to HPV
- No screening test
  - No endpoint in clinical trials
  - Late stage diagnosis

http://www.ghorayeb.com/OropharyngealCarcinoma.html
9-valent vaccine is estimated to prevent:
85% of cervical, 70% of oropharyngeal, 80% of anal, and 60% of penile cancers
Incidence of Diseases Covered in Adolescent Vaccine Series, US

Annual Incidence (per 100,000)

- Meningococcal Disease (all serogroups): 0.12
- Meningococcal Disease Serogroup B: 0.04
- Pertussis: 5.6
- Oropharyngeal Cancer (HPV-associated): 4.8
- Cervical Cancer (HPV-associated): 7.2


www.cdc.gov/mmwr/volumes/67/rr/mm6733a2.htm#T1_down
HPV vaccine is cancer prevention.

Talk to the doctor about vaccinating your 11–12 year old sons and daughters against HPV.

#UCanStopHPV
HPV vaccination eliminates HPV infection and the downstream consequences.

Source: Schiffman M et al., 2013
Decrease in HPV infections in the U.S. Pre-Vaccine Era, Early Vaccine Era and Later Vaccine Era

Study also found vaccine type HPV decreased 89% for vaccinated girls, and 34% for unvaccinated girls: indicates herd immunity

Decline in pre-cancer now impacting up to 30 yrs

Figure 1: Trends in prevalence rates of high grade histologically confirmed cervical abnormalities (CIN2+) diagnosed in Victorian women, Australia, by age group, 2000-2015

Updated from Brotherton et al. MJA 2016. Source VCCR
Zero Cases of HPV-Related Cancers in Vaccinated Women

<table>
<thead>
<tr>
<th>Malignancy</th>
<th>HPV Vaccinated women (65,565 person-years)</th>
<th>Non-vaccinated women (124,245 person-years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Rate (95% CI)</td>
</tr>
<tr>
<td>Cervix</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Vulva</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Oropharyngeal</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>All HPV associated cancers</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Breast</td>
<td>2</td>
<td>3. (0.8,12)</td>
</tr>
<tr>
<td>Thyroid</td>
<td>1</td>
<td>1.5 (0.2, 11)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>3</td>
<td>4.6 (1.5, 14)</td>
</tr>
<tr>
<td>Non-melanoma skin cancer</td>
<td>2</td>
<td>3.0 (0.8, 12)</td>
</tr>
</tbody>
</table>

Luostarinem, T. Vaccination protects against HPV-associated cancers. Int. J. Cancer 2018
EFFECTIVENESS DEPENDS ON TIMELY HPV VACCINATION
CDC/ACIP Recommendations

• Routine vaccination at age 11 or 12 years, can be started at age 9 years
  - Starting before 11 can improve completion

• Vaccination recommended
  o through age 26 for females
  o through age 21 for males
  o through age 26 for
    o men who have sex with men (MSM) or
    o Immunocompromised (including persons HIV-infected)

MMWR 2015;64:300-4
HPV Vaccine Recommendation

Girls & Boys can start HPV vaccination at age 9

Preteens should finish HPV vaccine series by 13th birthday

For girls 13-26 years old who haven’t started or finished HPV vaccine series

Plus boys 13-21 years old who haven’t started or finished HPV vaccine series
VACCINATING AT AGE 11-12 OR EVEN EARLIER

SHOW ME THE EVIDENCE
HIGHER ANTIBODY LEVELS
FEWER DOSES
MORE EFFECTIVE
Antibody response at age 9-13 vs. 16-26
Pre-teens need 2 doses 6-12 months apart

Age 15 and over need 3 doses over 6 months
Less than half of adolescents have annual visits starting earlier reduces missed opportunities.
Practice started vaccinating at age 9
Initiation improved for 9-12 year olds

Age 9 — +40%
Age 10 — +40%
Age 11 — +40%
Age 12 — +28%
Practice started vaccinating at age 9
Completion improved for 11-13 year olds

Age 13--↑10%
Age 12--↑20%
Age 11--↑35%
HPV VACCINE IS LONG-LASTING
Does immunity last?
Yes, 10 years and counting...

Follow-up through month 60

RESULTS: Antibody kinetics
- Similar in 2 groups
- Steady
- > Natural infection

2 doses (0, 6 mos) (ages 9-14 y)
3 doses (0, 1, 6 mos) (ages 15-25 y)
Natural infection

Antibody measured by ELISA
HPV 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
- 2018- similar chance of becoming pregnant
- 2018- ovarian insufficiency
- 2018- rheumatologic conditions

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

WHAT DO YOU SAY TO PARENTS?

HPV vaccine is cancer prevention.

Talk to the doctor about vaccinating your 11–12 year old sons and daughters against HPV.

#UCanStopHPV
Impact of Recommendation Quality

Vaccine initiation rates:

• 20%- 30% if no recommendation or presented as optional
• 50%, if low-quality recommendation
• 70-90%, if high-quality recommendation: *same way, same day*

Optional versus High Quality Recommendation

- **Optional:** “Have you thought about what shots you’d like to get today?”
  - May unintentionally imply shot is not important or few people do it
  - 20-30% vaccination rate in studies of both childhood and adolescent vaccines

- **High quality:** “We have some shots to do today”
  - Implies shot is important and most people get it
  - 70-90% vaccination rate in studies of both childhood and adolescent vaccines
Putting High Quality Recommendations into Practice: **Same Way, Same Day**

“Your child needs 3 vaccines today- Tdap, HPV and meningococcal”

*If starting before age 11, you can say:*

“Today, your child needs the HPV vaccine to protect him against cancers and other diseases caused by HPV.”
“I used to make the discussion of HPV a complex and time-consuming process. Typically I would say, ‘We have an excellent vaccine that prevents cancer, it’s not required for school but I highly recommend it.’ This would typically lead to additional conversation and a fair number of parents declining the vaccine. Then I changed my approach to say: “Your child is due for three vaccines today: TdaP, HPV, and MCV” and my decline rate was substantially lower! This was the approach I was already using for every other routine vaccine and was an easy change to make.”
What if a parent has questions?

What should you say?
Messages that make sense to parents

• HPV vaccine prevents cancer

• We give it at age 11 or younger because:
  – It works better
  – Younger kids have a better immune response
  – Younger kids need 2 shots instead of 3

• We like to start at age 9 because
  – Your child will get fewer shots at the 11 year old visit
    • Kids and parents really like this
IF A PARENT SAYS NO:
How to Handle Resistance:
Step 1 – Ask the parent to share concern(s)

Example:

“So you seem to have questions about the HPV vaccine. Asking questions is good! I want you to feel good about your decision, so let’s talk about it. Would you mind sharing what your particular concerns are?” (Note: non-threatening)

“Well, I’ve heard that it’s a vaccine to prevent a disease that’s transmitted by having sex, and she is a looooong way from having sex.”
How to Handle Resistance:  
Step 2 – Reflect, summarize, ask, advise

The provider reflects back what the parent is saying to be sure he/she understands (empathy) and summarizes what has been heard before proceeding, again with permission, to make a recommendation.

**Example:**

“So I can hear that you’re concerned that she’s too young for the HPV vaccine because HPV is transmitted by sexual activity. Well, I completely get that – she is only 11 after all. I’ve thought a lot about this. Is it okay if I go over how I’ve come to think about this vaccine?”
How to Handle Resistance: Step 3 – The crucial step

Example:

What NOT to say: “Well, data shows that many adolescents will be having sex by middle school, and if you’re worried about her having sex, studies have shown that it won’t increase the likelihood of her having sex.”

Do not try to use statistics like a battering ram in an emotional argument.
How to Handle Resistance: Step 3 – The crucial step

Example:

**What TO say:** “I used to think of this vaccine as something to prevent a sexually transmitted disease, but realized it’s really about preventing cancer.”

OR

“We recommend it at this age because younger kids have a better immune response. That’s why they need only 2 doses instead of 3.”

This avoids arguing as you have not contradicted the parent’s point.
How to Handle Resistance:  
Step 4 – Make a personalized recommendation

**Example:**

Parent’s Concern: “I heard about some bad side effects from the vaccine.”

Answer: “I’ve also seen things on social media, and I’m very happy to say that none of those things have been true when they’ve been investigated. In my practice, I’ve been giving the vaccine to my patients for more than 10 years now. I haven’t seen any serious side effects, and it is preventing precancers. Having said that, this is a decision that only you and your daughter can make. **What do you think?**”
If a Parent Declines...

- Declination is not final. **The conversation can be revisited.**
  Declining = Delaying

- May agree to vaccination later

- End the conversation with **at least 1 action** you both agree on.

- Many parents who decline at first will vaccinate later
Adolescent Vaccination Coverage with Tdap, MenACWY, and HPV, Massachusetts, NIS, 13-17 years, 2008 – 2017

WE ARE GETTING THERE!

Numbers in parentheses indicate a change from the previous year

*HPV Up to date (UTD): 2 doses if the first dose given before the 15th birthday and doses were separated by at least 5 months, otherwise, 3 doses

NIS Data, CDC
Expansion of HPV Vaccination to Age 45: will this prevent more cancer?

Adapted from Webinar given 10/29/18 with Debbie Saslow, PhD | Senior Director, HPV-related and Women’s Cancers, American Cancer Society & Vice Chair, National HPV Vaccination Roundtable

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How does vaccination of adult men and women compare to children?
Timeline

- October 5th, 2018: FDA approved Gardasil 9 for men and women ages 27-45 years
  - Based on safety and efficacy in a clinical trial

- February 27-28, 2018: ACIP presentations on additional evidence and economic analysis, potential vote considering
  - Disease burden
  - Effectiveness (in a real world setting)
  - Cost-effectiveness
Effectiveness and cost-effectiveness

- 11 studies from 6 countries
- 2/3 of studies showed no effectiveness or cost-effectiveness for women over age 20
Burden of Disease

- Vaccinating through at 26
  - Estimated to prevent at least 25,000 HPV-related cancers annually

- Vaccinating through age 45
  - Estimated to prevent only 193 more cancers
People want to know

- Is it safe?
- Does it work?
- Will my insurance pay for it?
HPV vaccination is safe for all ages

• Common side effects are a sore arm, and occasionally short-term fever or headache, similar to other vaccines

• No serious side effects have been reported caused by the vaccine for kids or adults

Castellague et al Br J Cancer, 2011
Parents may ask you

• Will it work for my child?

• Will it work for me?
HPV vaccination works REALLY WELL for kids…. But less well after age 20

Extremely low risk of pre-cancer for kids vaccinated on time

Castle, Prev Med, 2018
Not much cervical pre-cancer was prevented by vaccination in 27-45 year old women

- Lower risk in women without any infection
- No change when they looked at the entire study population (including those with previous infection)

Castellague et al Br J Cancer, 2011
Who is most likely to benefit?

1) Kids
2) Adults whose HPV risk approximates those of 11-12 year olds
Should you vaccinate the whole family?

Kids should all be Vaccinated. Clear evidence of benefit. Vaccine is safe.

Mom and dad can be vaccinated. Possible benefit by preventing HPV types they don’t have now but may be exposed to in the future. Vaccine is safe.
Putting it all together...

HPV is very common and causes bad disease

HPV vaccine is effective, long-lasting, and safe

Let’s work together to increase the number of patients who are protected
What is MA doing to prevent HPV cancers?
Activities in MA to Increase HPV Immunization Rates

- Provider education
  - Grand rounds, conferences, multi-media campaign with MDPH, Massachusetts Chapter of the AAP (MCAAP), Team Maureen, ACS, and other local partners
  - Keynote at Pediatric Immunization Conference on Achieving High HPV Vaccination Coverage at the practice level
  - Encourage vaccination beginning at ages 9 or 10
- Message Coordination
  - Work with a wide range of provider types, including pediatricians, nurses, medical assistants, local public health, dental professionals, and school nurses to ensure a consistent message of cancer prevention
- AFIX program
  - MDPH and MCAAP Faculty participate in physician-to-physician, practice-based quality improvement with an HPV focus
- Multi-component intervention at local FQHCs funded by ACS, also expanded nationally through HPV VACs project
Thank you! Questions? HPV Resources

National HPV Vaccine Roundtable:  http://hpvroundtable.org/
CDC main site:  https://www.cdc.gov/hpv/
CDC Top 10 List for HPV VaxSuccess: Attain and Maintain High HPV Vaccination Rates 5/18

CDC Tips and Timesavers – CDC  5/18

MDPH HPV Information Sheet
https://www.mass.gov/doc/mdph-hpv-information-sheet/download

MA ASTHO HPV Infographic

CDC Here’s How I Recommend Video Series
https://www.cdc.gov/hpv/hcp/how-i-recommend.html

Clinician & Health Systems Action Guides, National HPV Roundtable
http://hpvroundtable.org/action-guides/

Best  Provider HPV Resources Available at MCAAP HPV Website: https://mcaap.org/immunization-initiative/immunization-hpv/
EXTRA SLIDES
### Duration of Efficacy

| BASE TRIAL | | | | | Long-term follow-up available (planned) |
|---|---|---|---|---|
| **Trial** | **Participants age (years)** | **Trial duration (years)** | **Reference** |
| HPV 4v phase III efficacy | Females 15-26 | 4 | FUTURE II, NEJM 2007 | 10 (14) |
| HPV 4v phase III efficacy | Males 16-26 | 3 | Giuliano, NEJM 2011 Palefsky, NEJM 2011 | 8.5 (10) |
| HPV 4v phase III efficacy | Females 24-45 | 4 | Castellsague, Br J CA 2011 | 7.2 (10) |
| 9vHPV phase III efficacy | Females 16–26 | 4 | Joura, NEJM 2015 | - (14) |
| 9vHPV immunogenicity | Females/males 9–15 | 3 | Van Damme Pediatr 2015 | - (10) |
4vHPV efficacy trial in women 16–23 years
**Interim 10 year follow-up (14 years planned)**

Base RCT included >12,000 women from 13 countries
Follow-up in Nordic Cancer Registries, ~3,800 participants
Registry searches every 2 years

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>N cases/n subjects</th>
<th>Person-yrs at risk</th>
<th>Incidence / 100 person years at risk % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV 6/11/16/18-related CIN and vulvar/vaginal cancer</td>
<td>1/2171</td>
<td>10483</td>
<td>0 (0-0.1)</td>
</tr>
<tr>
<td>Time since day 1:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 4 years</td>
<td>0/2050</td>
<td>861</td>
<td>0 (0-0.4)</td>
</tr>
<tr>
<td>4-6 years</td>
<td>0/2168</td>
<td>4257</td>
<td>0 (0-0.1)</td>
</tr>
<tr>
<td>6-8 years</td>
<td>1/2059</td>
<td>3649</td>
<td>0 (0-0.2)</td>
</tr>
<tr>
<td>8-10 years</td>
<td>0/1439</td>
<td>1686</td>
<td>0 (0-0.2)</td>
</tr>
</tbody>
</table>

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

2. Kjaer, EUROGIN 2015
HPV Prophylactic Vaccines

- Recombinant L1 capsid proteins that form “virus-like” particles
- No DNA, no RNA
  - Non-infectious
  - Non-oncogenic
- Produce higher levels of neutralizing antibody than natural infection
Treatment of cervical precancerous lesions can lead to increased risk of preterm delivery

- 333,000 women undergo cone/LEEP procedures annually
- LEEP/HPV infection is associated with obstetric morbidity
  - Preterm delivery
  - Preterm rupture of membranes
  - Low birth weight
  - Long term developmental outcomes
  - Neonatal intensive care costs
### Cancers Caused by HPV per Year, U.S., 2011–2015

<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></td>
<td>Female</td>
</tr>
<tr>
<td>Cervix</td>
<td>91%</td>
<td>11,866</td>
</tr>
<tr>
<td>Vagina</td>
<td>75%</td>
<td>846</td>
</tr>
<tr>
<td>Vulva</td>
<td>69%</td>
<td>3,934</td>
</tr>
<tr>
<td>Penis</td>
<td>63%</td>
<td>0</td>
</tr>
<tr>
<td>Anus*</td>
<td>91%</td>
<td>4,333</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>70%</td>
<td>3,412</td>
</tr>
<tr>
<td>TOTAL</td>
<td></td>
<td>24,391</td>
</tr>
</tbody>
</table>

*Includes anal and rectal squamous cell carcinomas