An update on the Human Papillomavirus Vaccines

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I have no financial conflicts of interest

Objectives

#1 Understand the current state of knowledge about efficacy and safety of the 3 FDA-approved HPV vaccines

#2 Review what is known about the population impact of HPV vaccination

#3 Review CDC guidelines for whom/how to vaccinate

Case 1

A 23 year old woman has just moved to San Francisco and comes to you to establish Gyn care. She says she got one shot of an HPV vaccine (she doesn't know the name) before she went to college and never followed up to get the rest.

How would you advise her?
Case 2
A 45 year old G4P2 woman with a history of normal Paps has low grade SIL on her most recent Pap. She asks whether she should receive the HPV vaccine.

How would you advise her?

Case 3
The mother of a 12 year old has just heard on CNN that only 2 shots of the HPV vaccine are now needed. Her daughter had her first shot 2 months ago and just got the second shot last week. She asks you whether her daughter will need the 3rd shot.

How would you advise her?

Human Papillomaviruses
- Common DNA virus that infects skin, causes warts and other skin conditions
- >170 types of HPV
- >30 types infect genital skin (cervix, vagina, vulva, anus, penis, scrotum)
- 14-18 types are associated with cancer

Clinical Burden of HPV Disease
- Cervical cancer (70% are HPV 16 or 18)
- Genital warts (most are HPV 6 and 11)
- Cervical precancer
- Vulvar cancer and precancer
- Vaginal cancer and precancer
- Anal cancer and precancer
- Oropharyngeal cancers
- Laryngeal papillomatosis
L1 protein self-assembles into virus-like particles (VLPs)
- VLPs are immunogenic
- Antibodies to VLPs neutralize viral infectivity

FDA-approved HPV vaccine products

**Bivalent (2vHPV):** HPV16 and 18

**Quadrivalent (4vHPV):** HPV 6, 11, 16 and 18

**9-valent (9vHPV):** HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58

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**Trial populations**

<table>
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<tr>
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<th>Quadrivalent and 9-valent vaccines</th>
<th>Bivalent vaccine</th>
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<td><strong>Age</strong></td>
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<td><strong>Detection of genital warts at enrollment</strong></td>
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**Vaccine trial populations and outcomes**

- **Intention to treat population (ITT)**
- **Total vaccinated cohort (TVC)**
- **HPV Naive population**
- Disease associated with HPV vaccine types
- Disease associated with any HPV type
Naïve to 14 oncogenic HPV types

Efficacy against CIN 3+ associated with HPV 16/18: 100%

Efficacy against CIN3+ regardless of associated HPV types: 45.7%

Total vaccinated cohort

Lehtinen et al, Lancet Nov 2011

Efficacy: bivalent vaccine

Naïve to 14 HPV types

Efficacy against CIN 3 associated with HPV 6/11/16/18: 100%

Efficacy against CIN3 regardless of associated HPV types: 45.3%

Intention to treat pop'n

Munoz et al JNCI 2009

Efficacy: Quadrivalent vaccine

Naïve to 14 HPV types

Efficacy against external genital warts associated with HPV 6/11/16/18: 79.5%

Efficacy against external genital warts regardless of associated HPV types: 62%

Munoz et al JNCI 2009

Efficacy: genital warts in females

Intention to treat pop'n

Naïve to 14 HPB types

79.5%
(73-85)

62%
(53-69)

Efficacy: genital warts in males

Total vaccinated cohort

Efficacy against external genital lesions associated with HPV 6/11/16/18: 65.5%

Efficacy against external genital lesions regardless of associated HPV types: 60.2%

Giuliano et al, NEJM 2011

Efficacy: genital warts in males

Naïve to 14 HPV types

65.5%
(53-69)

83.8%
(74-88)

90.4%
(92-99)

96.4%
(92-99)
Naïve to 14 HPV types

Efficacy against anal intraepithelial neoplasia associated with HPV 6/11/16/18:
- 77.5% efficacy
- 50.3% efficacy

Efficacy against anal intraepithelial neoplasia regardless of associated HPV types:
- 54.9% efficacy
- 25.7% efficacy

Palefsky et al., NEJM 2011

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**9-valent HPV vaccine**

- This vaccine adds coverage to 5 HPV types: HPV 31, 33, 45, 52, 58
- About 14% of HPV-associated cancers in females (approximately 2800 cases annually) and 4% of HPV-associated cancers in males (approximately 550 cases annually) are caused by the 5 additional types in the 9-valent HPV vaccine.

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**9-valent vaccine trial results:**

- Both vaccines (4vHPV and 9vHPV) showed similar immunogenicity for responses to HPV 6, 11, 16, 18
- Both vaccines showed similar efficacy for disease related to HPV 6, 11, 16, 18

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**9-valent HPV vaccine**

- The primary efficacy analysis was comparing the 9-valent to the 4-valent HPV vaccine for incidence of high grade cervical, vulvar and vaginal disease related to HPV 31, 33, 45, 52 and 58
- Study endpoint related to HPV 6, 11, 16 and 18 outcomes was comparison of immunogenicity to see if both vaccines produced similar antibody titers
9-valent vaccine trial results:

- In the “HPV naïve” population, the 9vHPV vaccine reduced the risk of high grade cervical/vulvar/vaginal disease related to HPV 31, 33, 45, 52, 58 by **97%**

9-valent vaccine trial results

- In the overall trial population (HPV-infected and uninfected), there was no difference in the risk of high grade cervical/vulvar/vaginal disease by vaccine type (risk reduction 0.7%, 95% CI -16 to 15)

Safety

- Vaccines are associated with local reactions including pain, erythema and swelling, as well as systemic reactions such as fatigue, headache and myalgia
- No obvious safety issues were identified in Phase III trials
- 9vHPV had higher rate of injection site adverse events that 4vHPV (90.7 versus 84.9)

Summary: Objective #1

- All of the vaccines provide near 100% protection against infection the target HPV types in those who have not been previously exposed to those types
- Efficacy is attenuated in HPV-exposed populations
- These results led to target ages for vaccination being 11-12 year olds
Objective #2: Population-level impact of HPV vaccinations
• Systematic review and meta-analysis of time-trend studies that measured changes in prevalence or incidence of HPV-related endpoints: HPV infection, anogenital warts, and high grade cervical lesions (n=20 studies)
• Only bivalent and qHPV vaccines were studied
  Drolet et al, Mar 2015 NEJM

Vaccine impact on HPV infections:
• In 13-19 year old females: significant 64% reduction in prevalence of HPV types 16/18 in post-vaccine era compared to prevaccine
• In 20-24 year olds: reduction was lower (31%) and not quite statistically significant

Vaccine impact on HPV infections:
• In 13-19 year old females: prevalence of HPV types 31/33/45 was reduced significantly by 28%

Vaccine impact on HPV infections:
• The authors noted a small but non-significant increase in non-vaccine high risk HPV types in 20-24 year old women (RR 1.09, 95% CI 0.98-1.22), supporting continued monitoring to identify any signal of type-replacement
Vaccine Impact on Genital Warts

- In 15-19 year old females, anogenital warts decreased significantly by 31%.
- In 20-39 year old females, non-significant decreases were recorded (RR 0.9, 95% CI 0.8 to 1.02) but the reduction became significant in countries with high qHPV vaccine coverage (RR 0.7, 95% CI 0.5 to 0.9).

- In 15-19 year old males, there was no significant effect on genital warts except in countries with high female qHPV vaccine coverage (34% reduction, RR 0.7, 95% CI 0.5-0.9).
- No changes in wart incidence in 20-39 years old males.

Vaccine Impact on High Grade Cervical Lesions

- In 15-19 year old females, only one study had looked at this outcome and reported a significant decrease (RR 0.7, 95% CI 0.66-0.73).
- No significant change was noted in 2 studies reporting in 20+ year old females.

Summary: Objective #2 Population Impact

- Promising results to date in younger populations of vaccine impact for reduction of HPV infections and genital warts.
- Effects more pronounced in populations with high vaccine uptake.
- Full population impact will not be apparent for many years/decades.
- Effect on cancer reduction is not yet unknown.
Objective #3: CDC Recommendations for Use

- ACIP (CDC) recommends that routine HPV vaccination be initiated at age 11 or 12 years.
- The vaccination series can be started beginning at age 9 years.

CDC Recommendations for Use

- Vaccination is also recommended for females aged 13 through 26 years and for males aged 13 through 21 years who have not been vaccinated previously or who have not completed the 3-dose series
- Males aged 22 through 26 years may be vaccinated.

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- Males aged 22 through 26 years may be vaccinated.

CDC Recommendations for Use

- Vaccination of females is recommended through age 26 years for men who have sex with men and for immunocompromised persons (including those with HIV infection) if not vaccinated previously

CDC Recommendations for Use

- Vaccination of females is recommended with 2vHPV, 4vHPV (as long as this formulation is available), or 9vHPV.
- Vaccination of males is recommended with 4vHPV (as long as this formulation is available) or 9vHPV.
CDC: Vaccine administration

- 2vHPV, 4vHPV, and 9vHPV are each administered in a 3-dose schedule. The second dose is administered at least 1 to 2 months after the first dose, and the third dose at least 6 months after the first dose.

MMWR March 27, 2015 / 64(11);300-304

CDC: Future Policy Issues

- A clinical trial is ongoing to assess alternative dosing schedules of 9vHPV. ACIP will formally review the results as data become available.

MMWR March 27, 2015 / 64(11);300-304

- On October 7, 2016, the U.S. Food and Drug Administration (FDA) approved adding a 2-dose schedule for 9-valent HPV vaccine (Gardasil® 9) for adolescents ages 9 through 14 years.
CDC and ACIP review

• two doses of HPV vaccine in younger adolescents (aged 9-14 years) produced an immune response similar or higher than the response in young adults (aged 16-26 years) who received three doses.

CDC recommendation

• Two doses of HPV vaccine given at least six months apart at ages 11 and 12 years will provide safe, effective, and long-lasting protection against HPV cancers.
• Adolescents ages 13-14 are also able to receive HPV vaccination on the new 2-dose schedule.

CDC News release Oct 19, 2016

CDC recommendation

• Teens and young adults who start the series later, at ages 15 through 26 years, will continue to need three doses of HPV vaccine to protect against cancer-causing HPV infection.

CDC News release Oct 19, 2016

CDC and ACIP review

• CDC will provide guidance to parents, healthcare professionals, and insurers on the change in recommendation.
• CDC encourages clinicians to begin implementing the 2-dose schedule in their practice to protect their preteen patients from HPV cancers.

CDC News release Oct 19, 2016
### CDC: Vaccine Administration

- If the vaccine schedule is interrupted, the vaccination series does not need to be restarted.

**MMWR March 27, 2015 / 64(11);300-304**

### CDC: Vaccine Administration

- If vaccination providers do not know or do not have available the HPV vaccine product previously administered, or are in settings transitioning to 9vHPV, any available HPV vaccine product may be used to continue or complete the series for females for protection against HPV 16 and 18; 9vHPV or 4vHPV may be used to continue or complete the series for males.

**MMWR March 27, 2015 / 64(11);300-304**

### CDC: Precautions and Contraindications

- 4vHPV and 9vHPV are contraindicated for persons with a history of immediate hypersensitivity to yeast.
- 2vHPV should not be used in persons with anaphylactic latex allergy.

**MMWR March 27, 2015 / 64(11);300-304**

### CDC: Precautions and Contraindications

- HPV vaccines are not recommended for use in pregnant women

- If a woman is found to be pregnant after initiating the vaccination series, the remainder of the 3-dose series should be delayed until completion of pregnancy.

**MMWR March 27, 2015 / 64(11);300-304**
**CDC: Precautions and Contraindications**

- Pregnancy testing is not needed before vaccination. If a vaccine dose has been administered during pregnancy, no intervention is needed.
- A new pregnancy registry has been established for 9vHPV.
- Pregnancy registries for 4vHPV and 2vHPV have been closed with concurrence from FDA.

**CDC: Cervical Cancer Screening**

- Cervical cancer screening is recommended beginning at age 21 years and continuing through age 65 years for both vaccinated and unvaccinated women. Recommendations will continue to be evaluated as further post licensure monitoring data become available.

**CDC supplemental information and guidance**

- If a person desires protection against the 5 additional types prevented by the 9-valent HPV vaccine and has started a series with another HPV vaccine product, what issues should be considered?


**CDC supplemental information and guidance**

- The majority of all HPV-associated cancers that can be prevented by vaccination are due to HPV 16 and 18. These are the HPV types prevented by all three vaccines: bivalent vaccine, quadrivalent vaccine and 9-valent vaccine.
CDC supplemental information and guidance

- The benefit of protection against the 5 additional types targeted by 9-valent HPV vaccination is mostly limited to females for prevention of cervical cancers and precancers. This is because only a small percentage of HPV-associated cancers in males is due to the 5 additional types in 9-valent HPV vaccine.

CDC supplemental information and guidance

- Available data show no serious safety concerns in persons who were vaccinated with 9-valent HPV vaccine after having received a 3-dose series of quadrivalent HPV vaccine at least 12 months earlier.

CDC supplemental information and guidance

- There is no ACIP recommendation for routine additional 9-valent HPV vaccination of persons who previously completed a quadrivalent or bivalent vaccination series.

Are there populations of women unlikely to benefit from HPV vaccination?
Women with persistent HPV infection?

- Women who were seropositive and DNA positive for vaccine HPV types at enrolment showed an INCREASED risk of CIN2+ in the vaccine groups compared to the placebo group.
- Bivalent efficacy: risk reduction -13.8% (95% CI: -78 to 27).
- Quadrivalent vaccine: risk reduction -20% (95% CI <0 to 20).

Women with HPV infection?

- In the 9-valent vaccine trial, women who were HPV-infected on day 1*: relative risk CIN 2+: -11.3% (95% CI -40 to 11).
  
  * related to the 9 vaccine-related HPV types.

Women with HPV infection

- There may be historical risk factors or clinical findings that enrich for the group of women unlikely to benefit from vaccination (e.g., abnormal cytology).
- Prior CDC guidelines (2014) stated that prevaccination assessments (e.g., Pap testing or screening for high-risk HPV DNA, type-specific HPV DNA tests, or HPV antibody tests) to establish the appropriateness of HPV vaccination are not recommended.

Effect of Abnormal Pap on Vaccine Efficacy

- In a pooled analysis of the 4vHPV vaccine, vaccine efficacy (reduction of CIN2+) was 69% (stat significant) in women with a normal Pap on Day 1, but reduction was 16% (not stat significant) in those with an abnormal Pap on Day 1.

Kjear et al, 2009 Can Prev Res
Effect of Abnormal Pap on Vaccine Efficacy

• In a study of vaccine efficacy in North American trial participants, vaccine efficacy was 40% (stat significant) in women with normal cytology on Day 1, and was <0% (not stat sig) in women with abnormal cytology
  – Barr et al, 2008, AJOG

Use of vaccine in women with active HPV disease:

• FDA labeling specifically states “Gardasil is not intended to be used for treatment of active external genital lesions; cervical, vulvar, vaginal, and anal cancers; CIN; VIN; VaIN, or AIN.” Similar language is included in the labeling for the nonavalent HPV vaccine.

Use of vaccine in women with active HPV disease:

• The bivalent vaccine labeling states: “CERVARIX has not been demonstrated to provide protection against disease from vaccine and non-vaccine HPV types to which a woman has previously been exposed through sexual activity.”

Vaccination of older women

• Data about vaccine efficacy in women over the age of 26 is either not available (bivalent or nonavalent) or show lack of overall efficacy for CIN2+ (quadrivalent)
• FDA labeling specifically states that “Gardasil has not been demonstrated to prevent HPV-related CIN 2/3 or worse in women older than 26 years of age.”
Summary of CDC recommendations

- Target group for vaccination is adolescent boys and girls before the onset of sexual activity (i.e., before exposure to HPV)
- Vaccination beyond the age of 26 is not recommended
- New data support 2 doses ≥ 6 months apart in 11-14 year olds

Case 1

- A 23 year old G0 woman has just moved to San Francisco and comes to you to establish Gyn care. She says she got one shot of an HPV vaccine (she doesn’t know the name) before she went to college and never followed up to get the rest.
- How should you advise her about completing the vaccine series?

Which statement is true?

A. She needs to start the series over so that she gets the full 3 doses on the right schedule.
B. She only needs 2 more shots, but we need to find the name of the vaccine she already got so that we give her the same one.
C. She only needs 2 more shots, with the vaccine stocked in your office.
D. Given the new recommendations, she only needs one more shot.

Case 2

A 45 year old G4P2 woman with a history of normal Paps has low grade SIL on her most recent Pap. She asks whether she should receive the HPV vaccine. How should you advise her?
Which statements is true?

A. The CDC recommends vaccination in women at all ages if they request it
B. The HPV vaccine is for prevention, not for treatment, of HPV infection
C. Vaccination could help her body clear the HPV that is causing the abnormal Pap
D. She should receive the 9-valent vaccine because it provides broader protection

Case 3

- The mother of a 12 year old girl has just heard on CNN that now only 2 shots of the HPV vaccine, not 3, are being recommended. Her daughter had her first shot 2 months ago and just got the second shot last week. She asks you whether her daughter will need the 3rd shot.

Which of the following statements is true?

A. If her daughter has had 2 shots, she doesn’t need the 3rd shot
B. She still needs one more shot 6 or more months after the first shot
C. It depends which vaccine she has received as to whether she needs the additional shot

Questions?
Length of follow-up

- Bivalent vaccine: mean follow-up was 34.9 years - 39.4 years
- qHPV vaccine: mean follow-up was 3.6 years [maximum 4.9 years]
- 9vHPV vaccine: primary efficacy endpoint has been published

HPV vaccine manufacturing

- Bivalent (2vHPV): Baculovirus encoding L1 in insect cells
- Quadrivalent (4vHPV): Saccharomyces cerevisiae (Baker's yeast), expressing L1
- 9-valent (9vHPV): Saccharomyces cerevisiae (Baker's yeast), expressing L1

HPV vaccine products

Bivalent (2vHPV): Cervarix (GSK)

Quadrivalent (4vHPV): Gardasil (Merck)

9-valent (9vHPV): Gardasil 9 (Merck)

HPV vaccine adjuvants

- Bivalent (2vHPV):
  - 500 µg aluminum hydroxide,
  - 50 µg 3-O-desacyl-4' monophosphoryl lipid A

  Quadrivalent (4vHPV):
  -225 µg amorphous aluminum hydroxyphosphate sulfate

  9-valent (9vHPV):
  -225 µg amorphous aluminum hydroxyphosphate sulfate
9-valent HPV vaccine

Efficacy against associated with HPV 31,33,45,62,58:
50.3%

Efficacy against anal intraepithelial neoplasia regardless of associated HPV types:
25.7%

77.5%

54.9%

Naïve to 14 HPV types

Palefsky et al, NEJM 2011

- They also did an analysis of changes in anogenital wart diagnosis in the first 4 years after the introduction of qHPV vaccine
Data from countries with high female vaccine coverage (≥50%)

These data indicate herd-immunity since males and older females were not being targeted for vaccination.

Data from countries with low female vaccine coverage (<50%)

The authors propose that the increases in genital warts may be due to changes in sexual activity over time, reflected in populations with low vaccine coverage.

Basic messages to patients about HPV vaccination:

- Neither vaccine will provide 100% protection against cervical cancer or precursors; women must continue to get regular cervical cancer screening.
- The likelihood of abnormal Pap test results, colposcopy and cervical therapies is reduced by vaccination but not eliminated.

Basic messages to patients about HPV vaccination:

- Vaccination is not recommended during pregnancy.
A Pooled Analysis of Continued Prophylactic Efficacy of Quadrivalent Human Papillomavirus (Types 6/11/16/18) Vaccine against High-grade Cervical and External Genital Lesions
