Summary and Future ACIP HPV Vaccine Workgroup Plans

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Summary: HPV type attribution in HPV-associated disease in the United States

- **CIN2+ lesions**
  - ~50% attributable to HPV16/18
  - ~25% attributable to 5 additional types in investigational 9-valent vaccine
  - Largest % of lesions in all racial/ethnic groups are attributable to HPV16/18
    - Larger % of lesions attributable to HPV16/18 among non-Hispanic white compared with non-Hispanic black and Hispanic women
- **HPV-associated cancers**
  - ~62% (range, 48% penile - 79% anal) attributable to HPV16/18
  - ~11% (range, 8% anal - 18% vaginal) attributable to the 5 additional types
  - Largest % of HPV-associated cancers in all racial/ethnic groups attributable to HPV16/18
    - No differences by race for cervical, vaginal, vulvar, penile or anal cancers
    - Smaller % of oropharyngeal cancers (OP) attributable to HPV among non-Hispanic blacks; among HPV positive OP cancers, smaller % to attributable HPV16/18

Summary: 9-valent vaccine clinical trial data

- **Pivotal efficacy study among females aged 16-26 years**
  - Non-inferior HPV 6/11/16/18 immunogenicity vs. HPV4
  - ~97% protection against HPV 31/33/45/52/58-related disease
- **Immunobridging studies in adolescents**
  - Non-inferior immunogenicity in adolescents vs. adults

Estimated ACIP timeline for consideration of investigational 9-valent HPV vaccine

ACIP Date	Topic
Oct 2013	Overview of 9-valent vaccine clinical program
Feb 2014	Attribution of types in HPV-associated disease Clinical trial data Efficacy, immunogenicity and safety: females 16-26 years Bridging immunogenicity: females and males 9-15 years
June 2014	Clinical trial data Concomitant administration 9-valent HPV vaccine among prior HPV4 recipients Health economics
Oct 2014	GRADE Clinical trial data Immunogenicity: males 16-26 years* Recommendation options and discussion
Feb 2015	Recommendations Vote and VFC

* if available

Considerations: 9-valent HPV vaccine

- Routine vaccination at age 11 or 12 years
- Vaccination of older females and males who were not vaccinated at the recommended age
  - The timing for consideration of males 16-26 years; anticipate that vaccine will not be licensed in this age group at time of first licensure.
- Vaccination of persons fully or partially vaccinated with HPV4

ACIP HPV vaccine workgroup activities

- Currently focusing on investigational 9-valent HPV vaccine
- Ongoing reivew of post-licensure safety and coverage data
- Future review of reduced dose schedules for HPV vaccination

Reduced dose schedules for HPV vaccine

- **Global interest in simplified schedules for HPV vaccine**
- **Available data on 2-dose schedules**
  - **Bivalent vaccine**
    - Immunogenicity studies
    - Post hoc evaluation of data from efficacy trial
  - **Quadrivalent vaccine**
    - Immunogenicity studies
    - Post licensure effectiveness evaluations
- **2-dose schedules**
  - Some jurisdictions are using 2-dose schedules in their national/provincial immunization programs
  - EMEA granted marketing authorization for Cervarix (GSK) as a 2-dose schedule (0, 6 months) for girls aged 9 to 14 years, December 2013

Updated HPV Vaccine ACIP Statement

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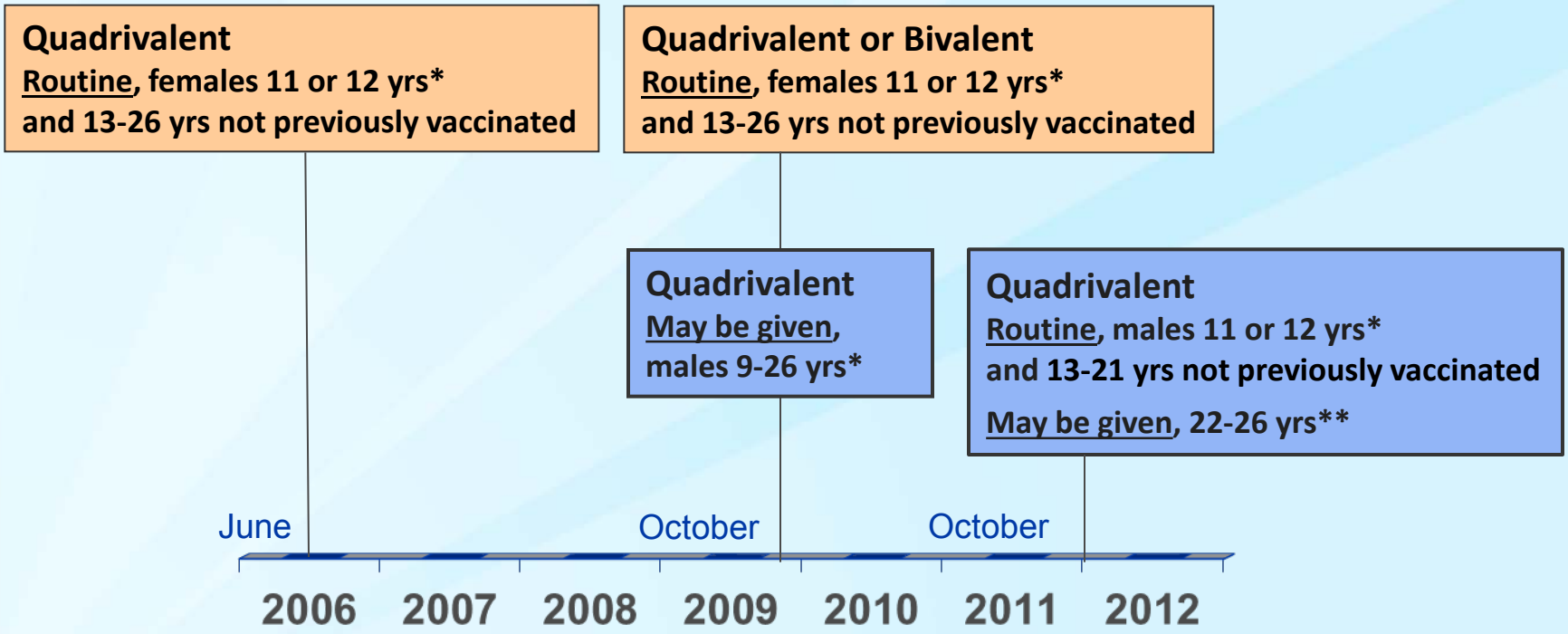
Evolution of recommendations for HPV vaccination in the United States



Quadrivalent (HPV 6,11,16,18) vaccine; Bivalent (HPV 16,18) vaccine

* Can be given starting at 9 years of age; ** For MSM and immunocompromised males, quadrivalent HPV vaccine through 26 years of age

Published ACIP recommendations for HPV vaccine

- **2007 ACIP Statement**
  - Recommendation for routine vaccination of females at age 11 or 12 years with quadrivalent HPV vaccine
- **2010 Policy Note**
  - Recommendation for routine vaccination of females with bivalent or quadrivalent HPV vaccine
- **2010 Policy Note**
  - Quadrivalent HPV vaccine may be given to males 9 through 26 years
- **2011 Policy Note**
  - Recommendation for routine vaccination of males at age 11 or 12 years with quadrivalent HPV vaccine
  - GRADE used for this recommendation

MMWR Recomm Rep 2007;56:1-24. MMWR 2010;59:626-9. MMWR 2010;59:630-2. MMWR 2011;60:1705-8.

Updated HPV Vaccine ACIP Statement

Objectives

- Consolidate recommendations for females and males
- Consolidate information and recommendations for bivalent and quadrivalent vaccines
- Harmonize wording that differed in policy notes/statement
- Update background information and data regarding efficacy, safety, immunogenicity, impact monitoring, etc.

Note

- Updated ACIP statement will facilitate efforts to develop future policy

Updated HPV Vaccine ACIP Statement: Sections included

- **Biology, immunology, epidemiology and natural history**
- **Clinical sequelae**
  - Cancers
  - Anogenital warts
  - Recurrent respiratory papillomatosis (RRP)
- **Prevention, treatment and cervical cancer screening**
  - Prevention of sexual transmission of HPV
  - Cervical cancer screening
  - Treatment of HPV disease
  - Selected health care and research laboratory workers

Updated HPV Vaccine ACIP Statement: Sections included

- **Vaccines**
  - Clinical trial data for quadrivalent and bivalent vaccines
  - Post licensure safety data
- **Economic burden of HPV disease and cost-effectiveness**
- **HPV vaccination program in the United States**
- **Summary of rationale for HPV vaccination recommendations**
- **Recommendations**
  - Routine
  - Administration: intervals, concomitant administration, interchangeability
  - Special populations
  - Precautions and contraindications

Updated HPV Vaccine ACIP Statement: Combined wording for male and female recommendations

- ACIP recommends routine vaccination at age 11 or 12 years with HPV4 or HPV2 for females and with HPV4 for males (male GRADE recommendation category: A, evidence type: 2). The vaccination series can be started beginning at age 9 years.
- HPV4 and HPV2 are each administered in a 3-dose schedule. The second dose should be administered 1-2 months after the first dose; the third dose 6 months after the first dose.
- Vaccination also is recommended for females aged 13 through 26 years and for males aged 13 through 21 years who have not been previously vaccinated or who have not completed the 3-dose series. Males aged 22 through 26 years may be vaccinated.

Updated HPV Vaccine ACIP Statement: Recommendation sections

- **Special populations**
  - Persons with abnormal Pap, anogenital warts, etc.
  - Immunocompromised persons
  - Men who have sex with men (MSM)
  - Lactating women
  - History of sexual abuse or assault

- **Precautions and contraindications**
  - Hypersensitivity or allergy
  - Acute illness
  - Preventing syncope
  - Pregnancy

Updated HPV Vaccine ACIP Statement: Special populations

- **Immunocompromised persons**

".....ACIP recommends routine vaccination at 11 or 12 years with HPV2 or HPV4 for females and with HPV4 for males. Vaccination is recommended through age 26 years for immunocompromised persons who have not been vaccinated previously or who have not completed the 3-dose series. "

- **Men who have sex with men (MSM)**

".....For MSM, ACIP recommends routine vaccination with HPV4, as for all males, and vaccination through age 26 years for those who have not been vaccinated previously or who have not completed the 3-dose series."

Updated HPV Vaccine ACIP Statement: Special populations

- **History of sexual abuse or assault**

"……While HPV vaccination will not promote viral clearance or protect against disease progression due to types already acquired, vaccination would protect against vaccine-preventable types not yet acquired. ACIP recommends HPV vaccination beginning at age 9 years for children and youth with any history of sexual abuse or assault who have not initiated or completed the 3-dose series. Adults through age 26 years who are victims of sexual abuse or assault should receive HPV vaccine if they have not already been vaccinated."

Updated HPV Vaccine ACIP Statement: Precautions and contraindications

- **Hypersensitivity or allergy to vaccine components**

"HPV vaccines are contraindicated for persons with a history of immediate hypersensitivity to any vaccine component. HPV4 is produced in *Saccharomyces cerevisiae* (baker's yeast) and is contraindicated for persons with a history of immediate hypersensitivity to yeast. Prefilled syringes of HPV2 have latex in the rubber stopper and should not be used in persons with anaphylactic latex allergy. ~~HPV2 single dose vials contain no latex~~"

Removed wording because only prefilled syringes available in the US.

Updated HPV Vaccine ACIP Statement: Precautions and contraindications

- **Pregnancy**

"HPV vaccines are not recommended for use in pregnant women. The vaccines have not been causally associated with adverse outcomes of pregnancy or adverse events in the developing fetus. However, if a women is found to be pregnant after initiating the vaccination series, the remainder of the 3-dose series should be delayed until completion of pregnancy…."

Updated HPV Vaccine ACIP Statement: Sections included

- **Monitoring impact of vaccination**
- **Areas of ongoing research and future priority activities**
  - A variety of issues mentioned very briefly, including the investigational 9-valent vaccine and reduced dose schedules

Comments from ACIP members and other reviewers

- Multiple small edits, clarifications
- Modification of wording in section on history of sexual abuse or assault, but no change in recommendation
- Additional data on post licensure safety evaluations

Table 8. Observational, population-based, post-licensure quadrivalent HPV (HPV4) vaccine safety studies among females aged 9–26 years — USA and other countries

System or review and Country	Doses evaluated	Description	Methods	Findings
Vaccine Safety Datalink (VSD)[a] USA	600,559	Large data base used for active surveillance and research. Safety assessment of 7 pre-specified health outcomes among HPV4 female recipients.	Cohort design with weekly sequential analyses of electronic medical data	No statistically significant increase in risk for the outcomes monitored.
Post-marketing commitment (to US FDA)[b] USA	346,972	General study assessment of HPV4 following routine administration at two large managed care organizations.	Self-controlled risk interval design supplemented with medical record review	HPV4 associated with syncope on the day of vaccination and skin infections in the two weeks after vaccination.[§] No other vaccine safety signals were detected.
Post-marketing commitment (to US FDA)[c] USA	346,972	Assessment of 16 pre-specified autoimmune conditions following routine use of HPV4 at two large managed care organizations.	Retrospective cohort using electronic medical data, supplemented with medical record review	No confirmed safety signals for monitored conditions.
Register based cohort study[d] Denmark and Sweden	696,240	Assessment of 23 different autoimmune, 5 neurologic conditions and VTE following HPV4 among females aged 10-17 years.	Retrospective cohort using national patient registers	No consistent evidence of causal associations between HPV4 and the events monitored.
Pharmacoepidiemiologic General Research Extension[e] France		Assessment of 6 different autoimmune outcomes among 211 cases and 875 controls aged 14-26 years.	Case control study with recruitment of cases and controls through registries	No increased risk of combined endpoint of 6 autoimmune disorders.

Table 8 references

[a]Gee J, Naleway A, Shui I, et al. Monitoring the safety of quadrivalent human papillomavirus vaccine: findings from the Vaccine Safety Datalink. Vaccine 2011;29:8270-8284.

[b]Klein NP, Hansen J, Chao C, et al. Safety of quadrivalent human papillomavirus vaccine administered routinely to females. Arch Pediatr Adolesc Med 2012;166:1140-1148.

[c]Chao C, Klein NP, Velicer CM, et al. Surveillance of autoimmune conditions following routine use of quadrivalent human papillomavirus vaccine. J Intern Med 2012;271:193-203.

[d]Arnheim-Dahlström L, Pasternak B, Svanström H, Sparén P, Hviid A. Autoimmune, neurological, and venous thromboembolic adverse events after immunisation of adolescent girls with quadrivalent human papillomavirus vaccine in Denmark and Sweden: cohort study. BMJ 2013 9;347:f5906.

[e]Grimaldi-Bensouda L, Guillemot D, Godeau B, et al. Autoimmune disorders and quadrivalent human papillomavirus vaccination of young female subjects. J Intern Med. 2013 (doi: 10.1111/joim.12155.)

Draft statement: summary

- Updates background data and clinical trial data
- Consolidates and clarifies existing recommendations
- Includes a variety of new sections
  - Post licensure safety data
- Recommendations will be updated in the future as more data become available

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