HPV Vaccination in the United States, the First 10 Years: Policy, Program and Monitoring

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Barriers in HPV Vaccination & Cervical Screening Programmes
27-28 June 2016
Antwerp, Belgium
Overview

- HPV vaccine policy
- United States vaccination program
- Post-licensure monitoring
  - Focus on safety
Evolution of Recommendations for HPV Vaccination in the United States

**Quadrivalent**
Routine, females 11 or 12 yrs* and 13-26 not previously vaccinated

**Quadrivalent or Bivalent**
Routine, females 11 or 12 yrs* and 13-26 not previously vaccinated

**Quadrivalent**
May be given, males 9-26 yrs*

**Quadrivalent**
Routine, males 11 or 12 yrs* and 13-21 not previously vaccinated**

**9-valent**
Recommended as 1 of 3 vaccines for females and 1 of 2 for males.

- 2006: Quadrivalent (HPV 6,11,16,18) vaccine; Bivalent (HPV 16,18) vaccine
- 2007: 9-valent (HPV 6,11,16,18 31.33, 45, 52, 58) vaccine
- 2008: Quadrivalent or Bivalent
- 2009: Quadrivalent or Bivalent
- 2010: Quadrivalent
- 2011: Quadrivalent
- 2012: Quadrivalent
- 2013: Quadrivalent
- 2014: Quadrivalent
- 2015: Quadrivalent

*Can be given starting at 9 years of age; **May be given, 22-26 yrs, recommended for MSM and immunocompromised males through 26 years of age
Recommendations for HPV Vaccination in the United States 2011 - Present

- Routine vaccination of girls and boys at age 11 or 12 years*
- Vaccination through age 26 for females and through age 21 for males, if not previously vaccinated
- Vaccination through age 26 for immunocompromised persons (including persons HIV-infected) and for men who have sex with men
- 3-dose schedule (0,1-2 and 6 months)

*The vaccination series can be started at age 9 years
Recommendations for HPV Vaccination in the United States 2011 - Present

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- 3-dose schedule (0,1-2 and 6 months)
- Updated in 2015 after licensure of 9vHPV

*The vaccination series can be started at age 9 years

Females: 2vHPV, 4vHPV or 9vHPV
Males: 4vHPV or 9vHPV
Upcoming policy considerations in the U.S. 2-dose HPV vaccination schedule

- **Regulatory approvals and recommendations outside of U.S.**
  - EMA approved 2-dose schedule (age 9–14 years for 2vHPV and 9–13 years for 4vHPV) in 2014 and for 9vHPV in 2016
  - WHO recommended 2-dose schedule for girls ages 9–13 years*

- **ACIP started review of 2-dose schedules in 2016**
  - Supplemental Biologics License Application submitted to FDA by manufacturer for 9vHPV 2-dose schedule in early 2016
  - Data presented from 9vHPV 2-dose trial - ACIP Feb 2016
  - Continued evidence review and GRADE - ACIP June 2016

*Weekly Epidemiologic Record 2014; 89: 221-236
EMA – European Medicines Agency; ACIP – Advisory Committee on Immunization Practices
Vaccine Regulatory Approval and Recommendations

- Food and Drug Administration licensure
- Advisory Committee on Immunization Practices (ACIP) recommendations
- Centers for Disease Control and Prevention (CDC) acceptance and publication in MMWR
- Financing and insurance coverage
  - Vaccines for Children Program (VFC) and Affordable Care Act (ACA)
Vaccine Financing

- Vaccines for Children (VFC) Program – established in August 1993, operational since October 1994
  - Unique statutory authority established by Omnibus Budget Reconciliation Act of 1993 (42 U.S.C. § 1396a) gives ACIP authority to determine vaccines provided in the VFC Program

- The Affordable Care Act (ACA) – enacted in 2010
  - Requires private insurance coverage for immunizations without copays/deductibles when provided by an in-network provider
  - Health plans have one plan year from MMWR publication to implement recommendations according to CDC Immunization schedules

http://www.cdc.gov/vaccines/programs/vfc/default.htm
VACCINATION PROGRAM IMPLEMENTATION
U.S. HPV Immunization Program

- Target age group 11 or 12 years
- One of several vaccines recommended for adolescent age group
  - Tetanus, diphtheria, acellular pertussis vaccine (Tdap),
  - Meningococcal (MCV4)
  - Influenza (annual)
- Vaccinations funded through public program for those eligible and through private insurance
- Vaccine delivered mainly by primary care providers
National Estimated Vaccination Coverage among Adolescents 13–17 Years, NIS-Teen 2006-2014

Routine recommendation for females

Routine recommendation for males

≥1 Tdap
≥1 MenACWY
≥1 HPV (F)
≥3 HPV (F)
≥1 HPV (M)
≥3 HPV (M)

MMWR 2015;64:784-792
Estimated Coverage with ≥ 1 Dose HPV Vaccine among Females and Males 13–17 Years by State, NIS -Teen 2014

NIS-Teen, National Immunization Survey - Teen
MMWR 2015;64:784-792
HPV Vaccination Coverage among Adolescents Aged 13-17 Years by Poverty Status NIS-Teen, United States, 2014

* Statistically significant difference compared with adolescents at or above the poverty level (p<0.05).

* Statistically significant difference compared with adolescents at or above the poverty level (p<0.05).

MMWR 2015;64:784-792
Actual and potentially achievable vaccination coverage of ≥1 HPV vaccine doses by age 13 among adolescent girls if missed opportunities* were eliminated, NIS-Teen 2007-2013 combined

*Missed opportunity defined as having a healthcare encounter where at least one vaccine was administered but HPV vaccine was not
### Top 5 reasons for not vaccinating daughter, among parents with no intention to vaccinate in the next 12 months, United States, 2013

<table>
<thead>
<tr>
<th>Reason</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Lack of knowledge</td>
<td>15.5%</td>
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<tr>
<td>Not needed or necessary</td>
<td>14.7%</td>
</tr>
<tr>
<td>Safety concern/side effects</td>
<td>14.2%</td>
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<tr>
<td>Not recommended by provider</td>
<td>13.0%</td>
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<tr>
<td>Not sexually active</td>
<td>11.3%</td>
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</tbody>
</table>
Strength of Provider* HPV Vaccine Recommendation for Female Patients, (N=609)

11-12 y.o. females
- Strongly recommend: 51%
- Recommend, but not strongly: 36%
- Make no recommendation: 8%

13-15 y.o. females
- Strongly recommend: 79%
- Recommend, but not strongly: 15%

16-18 y.o. females
- Strongly recommend: 85%
- Recommend, but not strongly: 10%

*pediatricians and family physicians

Allison et al. Acad Pediatr 2013
HPV Vaccine Communications During the Healthcare Encounter

- HPV vaccine is often presented as ‘optional’ whereas other adolescent vaccines are recommended.
- Some expressed mixed or negative opinions about the ‘new vaccine’ and concerns over safety/efficacy.
- When parents expressed reluctance, providers were hesitant to engage in discussion.
- Some providers shared parents’ views that teen was not at risk for HPV and could delay vaccination until older.

Strategies to Increase HPV Vaccination Coverage, United States

- Support state and local immunization programs
- Mobilize partners and stakeholders
- Strengthen provider commitment
- Improve and utilize systems
- Increase public awareness
2013/2014 PPHF HPV Immunization Awardees

**2013 Awardees**
- Minnesota
- Massachusetts
- New York
- New York City
- Philadelphia
- District of Columbia
- Ohio
- Chicago
- Georgia
- Utah
- Arizona

**2014 Awardees**
- Washington
- North Dakota
- Michigan
- Wisconsin
- Rhode Island
- Illinois
- Iowa
- Kentucky
- Kansas
- Nevada
- Alaska

Abbreviations:
PPHF = Prevention and Public Health Fund;
HPV = Human papillomavirus
HPV Immunization Awardee Activities 2013 and 2014 PPHF

- Developing a jurisdiction-wide joint initiative with immunization stakeholders
- Implementing a comprehensive communication campaign targeted to the public
- Using Immunization Information System-based reminder / recall for adolescents
- Using assessment and feedback to evaluate and improve the performance of immunization providers
- Implementing strategies targeted to immunization providers to:
  - Increase knowledge regarding HPV-related diseases and vaccine
  - Improve skills to deliver strong, effective vaccination recommendations
  - Decrease missed opportunities

PPHF - Prevention and Public Health Fund
HPV - Human papillomavirus
Assessment of the healthcare provider’s vaccination coverage levels and immunization practices

Feedback of results to the provider along with recommended quality improvement strategies to improve processes, immunization practices, and coverage levels

Incentives to recognize and reward improved performance

Exchange of information with providers to follow up on their progress towards quality improvement in immunization services and improvement in immunization coverage levels

http://www.cdc.gov/vaccines/programs/afix/index.html
Overview of AFIX

AFIX is a quality improvement program used by awardees to raise immunization coverage levels, reduce missed opportunities to vaccinate, and improve standards of practices at the provider level. The acronym for this four-part dynamic strategy stands for:

1. **Assessment** of the healthcare provider’s vaccination coverage levels and immunization practices.
2. **Feedback** of results to the provider along with recommended quality improvement strategies to improve processes, immunization practices, and coverage levels.
3. **Incentives** to recognize and reward improved performance.
4. **Exchange** of information with providers to follow up on their progress towards quality improvement in immunization services and improvement in immunization coverage levels.

Contacts

Quick Vaccine Information Links

What’s New!

- Quarterly Conference Call Minutes
  - March 26, 2015
- AFIX Policies and Procedures Guide
- AFIX Site Visit Questionnaire
- AFIX Site Visit Answer Guide

Resources for Awardees

- AFIX Site Visit Answer Guide
- AFIX Logic Model (updated Nov 2013)
Implementing Strategies Targeted to Immunization Providers

- HPV core messages
- You Are the Key clinician slides
- Provider Tip Sheet
- Provider Portal for HPV

HPV Vaccine Resources for Healthcare Professionals

Non-MD Clinicians’ Understanding of Human Papillomavirus (HPV) Vaccination Recommendations and Barriers

HPV Vaccine Key Points
POST-LICENSEURE MONITORING
Evaluation of HPV Vaccination Programs

- Coverage
- Attitudes and practices
- Safety
- Impact
Evaluation of HPV Vaccination Programs

- Coverage
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- Impact

- Safety monitoring infrastructure
- VAERS – overview
- Safety monitoring - 4vHPV vaccine
- Misuse of VAERS data
- Monitoring plans for 9vHPV
## Post-licensure Vaccine Safety Monitoring Infrastructure in the US

<table>
<thead>
<tr>
<th>System</th>
<th>Collaboration</th>
<th>Description</th>
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<tbody>
<tr>
<td>Vaccine Adverse Event Reporting System (VAERS)</td>
<td>CDC and FDA</td>
<td>US frontline spontaneous reporting system to detect potential vaccine safety problems</td>
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<tr>
<td>Vaccine Safety Datalink (VSD)</td>
<td>CDC and 9 Managed Healthcare Plans</td>
<td>Large linked database system used for active surveillance and research</td>
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<tr>
<td></td>
<td></td>
<td>~9.2 million members (~3% of US pop.)</td>
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<tr>
<td></td>
<td></td>
<td>- Conducts monitoring &amp; evaluation</td>
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<tr>
<td></td>
<td></td>
<td>- Rates &amp; risk estimates can be calculated</td>
</tr>
<tr>
<td>Clinical Immunization Safety Assessment (CISA) Project</td>
<td>CDC and 7 Academic Centers</td>
<td>Expert collaboration that conducts individual clinical vaccine safety assessments and clinical research</td>
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</tbody>
</table>
Vaccine Adverse Event Reporting System (VAERS)

- National spontaneous reporting system jointly administered by CDC and FDA since 1990 for adverse events† (AE) following vaccination
  - Accepts reports from healthcare providers, manufacturers and public
  - Not designed to assess causality
  - Signs/symptoms of AEs coded using MedDRA* preferred terms (PTs) and entered into database
  - More than one code may be assigned to a single event
  - Coded as serious if one of the following is reported
    - Death, life-threatening illness, hospitalization, prolongation of hospitalization, or permanent disability

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† Any untoward medical occurrence following vaccination and which does not necessarily have a causal relationship with vaccination

* Medical Dictionary for Regulatory Activities. Available at: http://www.meddra.org/
VAERS: National Spontaneous Reporting System Co-Administered by CDC and FDA

**Strengths**
- Rapid signal detection
- Can detect rare adverse events
- Generates hypothesis
- Encourages reports from healthcare providers and accepts reports from patients and others
- Data available to the public

**Limitations**
- Reporting bias (e.g., underreporting, stimulated reporting)
- Inconsistent data quality and completeness
- Not designed to assess if vaccine caused an adverse event (AE)
- Lack of unvaccinated comparison group
Post-licensure 4vHPV Vaccine Safety Monitoring

- **VAERS postlicensure safety summary (2009)**
  - Proportion of reports for venous thromboembolism (VTE) and syncope after 4vHPV were higher than expected
  - Updated reviews in 2013 and 2014--no new concerns identified

- **VSD conducted near-real time monitoring following 600,558 4vHPV doses (2011)**
  - No associations with Guillain-Barré Syndrome, stroke, appendicitis, seizures, syncope, allergic reactions, and anaphylaxis
  - Non-significant elevated risk (RR=1.98) for VTE in females 9–17 years

- **VSD study using self-controlled case series method**
  - No increased risk of VTE following 4vHPV among persons aged 9-26 years

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1 Slade et al, Postlicensure safety surveillance for quadrivalent human papillomavirus recombinant vaccine. JAMA 2009
4 Gee et al, Monitoring the safety of quadrivalent human papillomavirus vaccine: findings from the Vaccine Safety Datalink. Vaccine 2011
5 Relative risk calculated using Poisson based maximized sequential probability ratio test (maxSRPT)
Differences in VAERS Government Data vs. VAERS Public Data

- **Internal/Governmental:**
  - Includes report and follow up data* and personal identifiers
    - Hospital discharge data
    - Autopsy reports
    - Lab data
  - Updated daily

- **Public: includes report data, but not follow up data or any personal identifiers**
  - VAERS WONDER ([http://wonder.cdc.gov/vaers.html](http://wonder.cdc.gov/vaers.html))
  - Downloadable data files (Excel format) from VAERS website- [https://vaers.hhs.gov/data/index](https://vaers.hhs.gov/data/index)
  - Both public databases updated every 4-6 weeks

*Follow up data is collected only on serious non-manufacturer reports*
Examples of Misuse of VAERS Data

- Geier DA, Geier MR. A case-control study of quadrivalent human papillomavirus vaccine-associated autoimmune adverse events. Clin Rheumatol 2015;34:1225-31
  - Authors report a significant relationship between 4vHPV and serious autoimmune adverse events
  - Paper has many biases; most importantly using HPV reports to classify those into cases and controls

  - Paper does not adequately address the limitations of VAERS and makes inaccurate assumptions in their calculations; authors to conclude that rates of GBS are higher following 4vHPV when compared with other vaccines

  - The authors imply that Gardasil may exacerbate the disease and include VAERS data: "It is also of note that in the post-licensure period (2006–2011), the US VAERS received 360 reports of abnormal Pap smears, 112 reports of cervical cancer dysplasia, and 11 reports of cervical cancers related to HPV vaccines."
9vHPV Safety Monitoring and Evaluation

- **Postmarketing commitments by manufacturer**¹
  - Completion of two 10-year study extensions
    - Males and females 9-15 years
    - Females 16-26 years
  - Observational study to further characterize safety profile in ~10,000 persons
  - Pregnancy registry

- **FDA’s Sentinel Initiative pharmacovigilance plan**²
  - General safety study
  - Pregnancy outcomes study

- **CDC’s safety evaluation**
  - VAERS
  - Vaccine Safety Datalink (VSD)
    - Near real-time monitoring for pre-specified outcomes through Rapid Cycle Analysis

¹[http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm426520.htm](http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm426520.htm)
²[http://www.brookings.edu/~media/events/2015/02/05%20fda%20sentinel%20initiative%20workshop/2015%20sentinel%20initiative%20annual%20meeting%20slide%20deck.pdf](http://www.brookings.edu/~media/events/2015/02/05%20fda%20sentinel%20initiative%20workshop/2015%20sentinel%20initiative%20annual%20meeting%20slide%20deck.pdf)
United States

SUMMARY SWOT-ANALYSIS
**Strengths:**
- Evidence based recommendation process
- Financing of vaccine through public and private sector

**Weaknesses:**
- Delivery of vaccine through providers
- Strength of provider recommendations

**Opportunities:**
- Strengthening the ‘adolescent platform’ for vaccination
- Collaborations with partners on national and local level
- Sharing successes between program areas

**Threats:**
- Lack of strong provider recommendation
- Concerns about safety
- Anti-vaccine messages via internet and social media
Summary

- Vaccination recommendations have evolved since the first HPV vaccine licensed in 2006
- US HPV vaccine coverage increasing but remains; efforts to increase uptake ongoing
  - Main focus is on increasing strength of provider recommendation and elimination of missed opportunities
- In spite of low coverage, impact on early outcomes demonstrated
- U.S. has extensive safety monitoring in place for all vaccines
  - Many examples of misuse of publicly released VAERS data for HPV vaccine
- Vaccine policy will continue to evolve as new data are available from vaccine trials and from evaluation of vaccination programs
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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.
Prevalence of HPV in Cervicovaginal Swabs, by Age
NHANES 2003-2006 and 2009-2012

Markowitz et al. Pediatrics 2016