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

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Respiratory Diseases

Barriers in HPV Vaccination & Cervical Screening Programmes

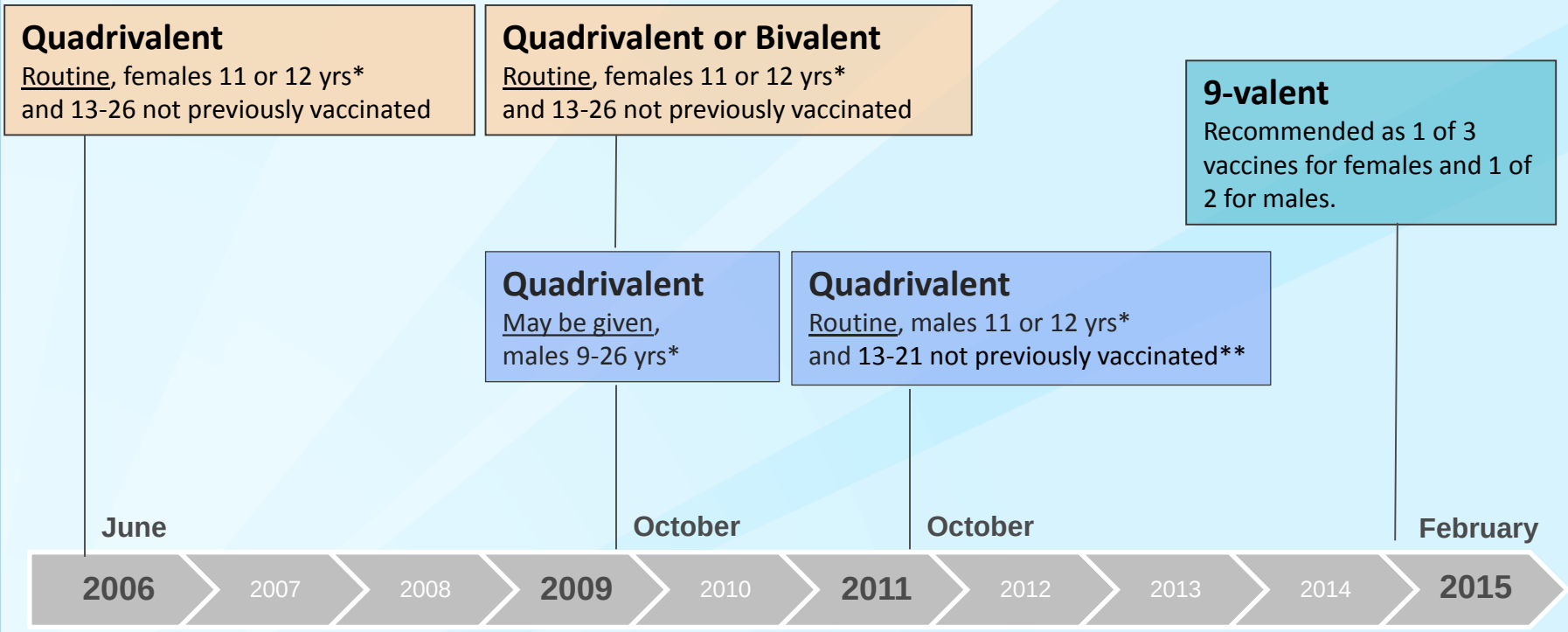
27-28 June 2016

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 (HPV 6,11,16,18) vaccine; Bivalent (HPV 16,18) vaccine; 9-valent (HPV 6,11,16,18 31.33, 45, 52, 58) vaccine

*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)

MMWR 2014;63:1-30

*The vaccination series can be started at age 9 years

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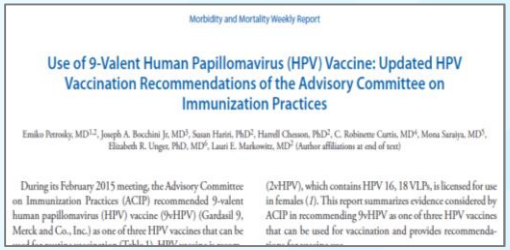
- 3-dose schedule (0,1-2 and 6 months)
- Updated in 2015 after licensure of 9vHPV


Morbidity and Mortality Weekly Report

Use of 9-Valent Human Papillomavirus (HPV) Vaccine: Updated HPV Vaccination Recommendations of the Advisory Committee on Immunization Practices

Emiko Petrosky, MD[1,2], Joseph A. Bocchini Jr, MD[3], Susan Hariri, PhD[2], Hamell Chesson, PhD[2], C. Robinette Curtis, MD[4], Mona Saraiya, MD[5], Elizabeth R. Unger, PhD, MD[6], Lauri E. Markowitz, MD[2] (Author affiliations at end of text)

During its February 2015 meeting, the Advisory Committee on Immunization Practices (ACIP) recommended 9-valent human papillomavirus (HPV) vaccine (9vHPV) (Gardasil 9, Merck and Co., Inc.) as one of three HPV vaccines that can be (2vHPV), which contains HPV 16, 18 VLPs, is licensed for use in females (1). This report summarizes evidence considered by ACIP in recommending 9vHPV as one of three HPV vaccines that can be used for vaccination and provides recommenda-

MMWR 2015;64:300-4

Females: 2vHPV, 4vHPV or 9vHPV
Males: 4vHPV or 9vHPV

MMWR 2014;63:1-30

*The vaccination series can be started at age 9 years

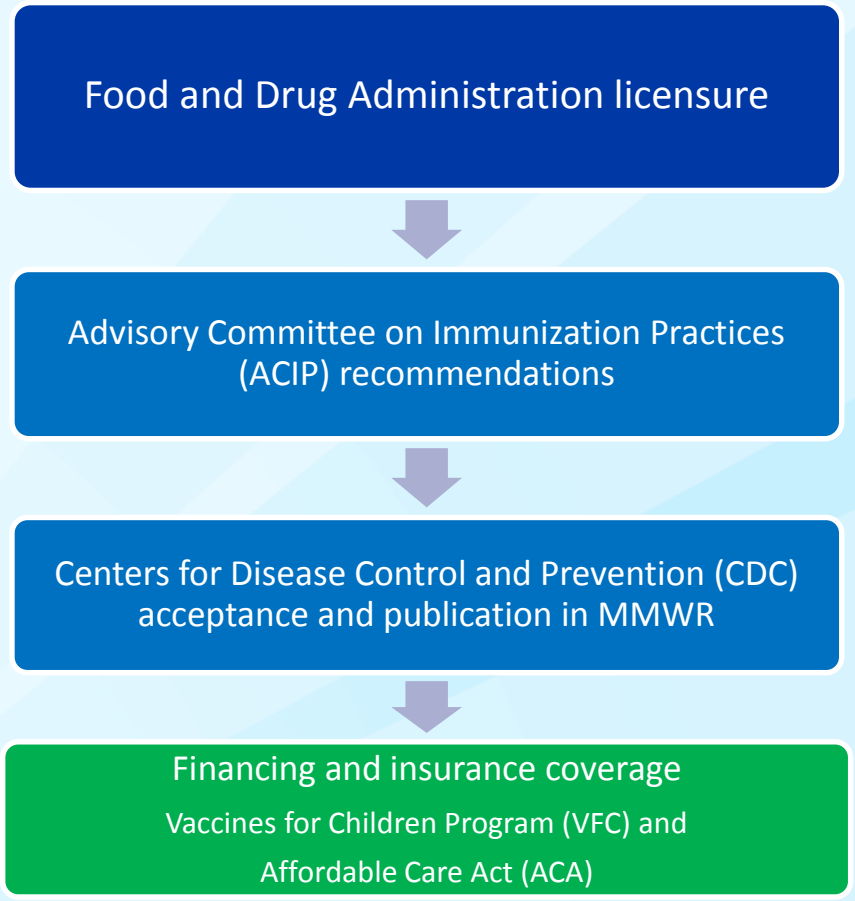
Upcoming policy considerations in the U.S. 2-dose HPV vaccination schedule

- **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



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***

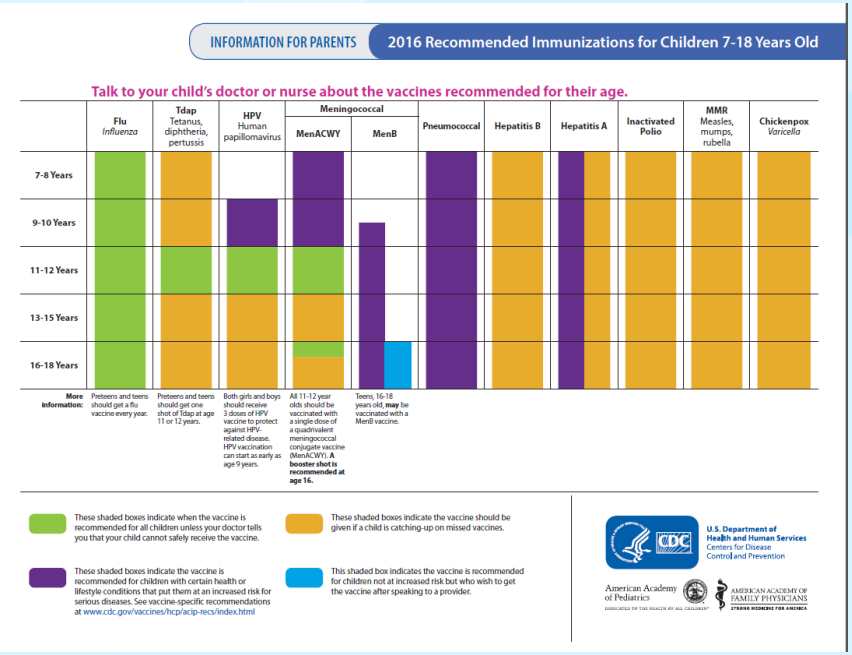
- **The Affordable Care Act (ACA) – enacted in 2010**
  - Requires private insurance coverage for immunizations without copays/deductibles when provided by an in-network provider
  - Health plans have one plan year from MMWR publication to implement recommendations according to CDC Immunization schedules

http://www.cdc.gov/vaccines/programs/vfc/default.htm

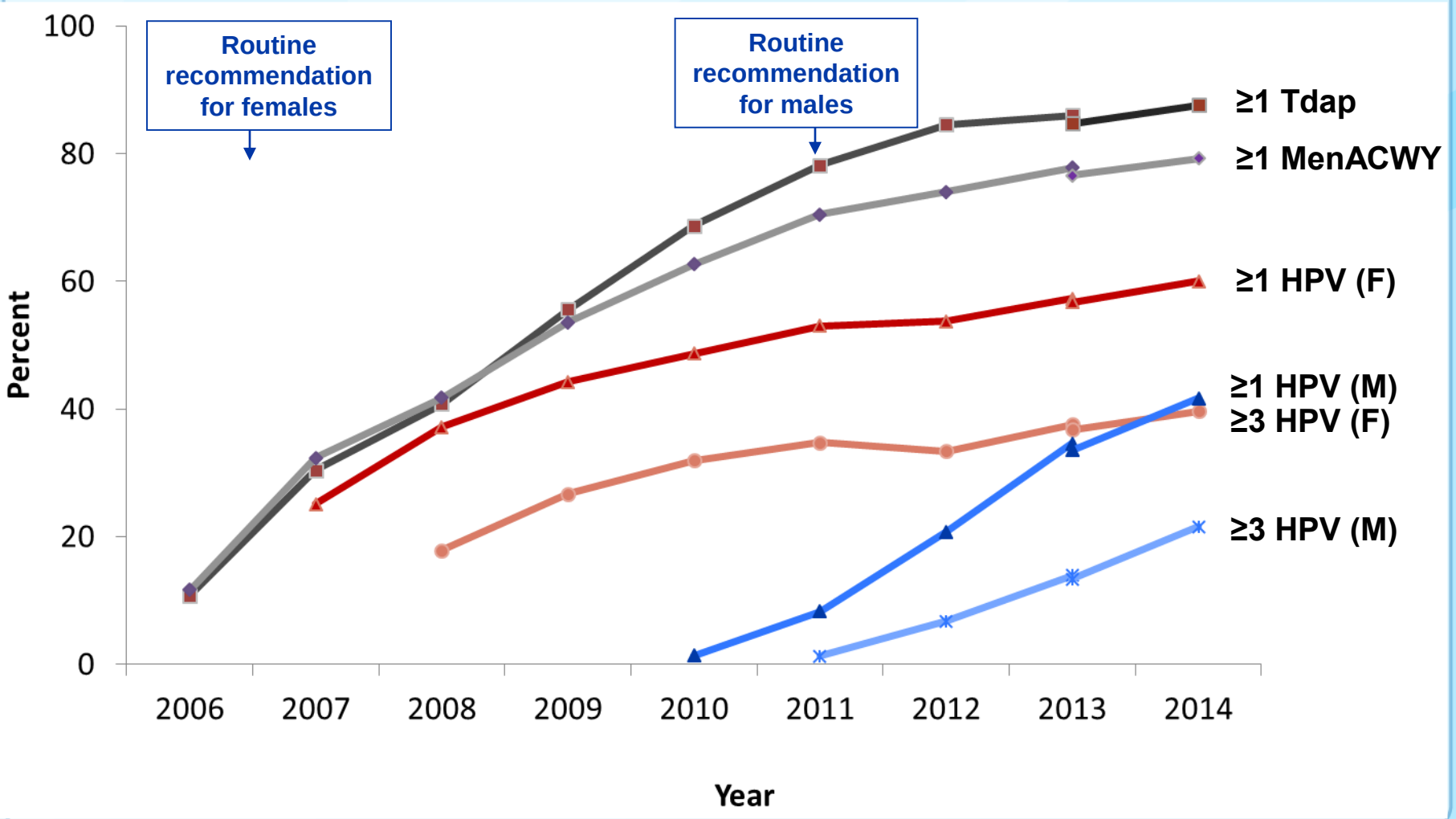
VACCINATION PROGRAM IMPLEMENTATION

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



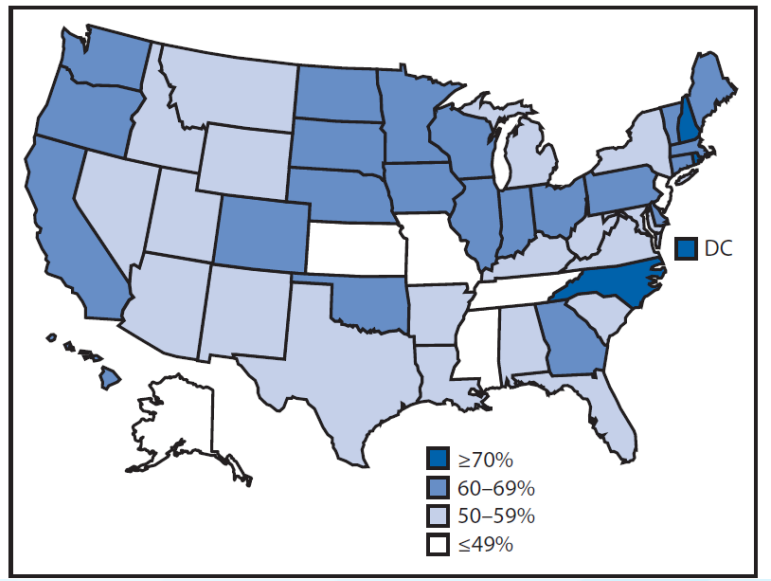
National Estimated Vaccination Coverage among Adolescents 13–17 Years, NIS-Teen 2006-2014



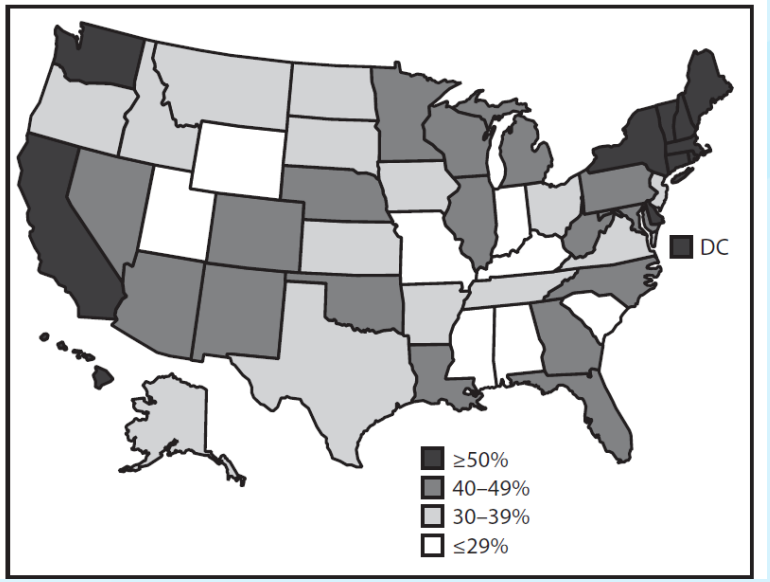
MMWR 2015;64:784-792

Estimated Coverage with ≥ 1 Dose HPV Vaccine among Females and Males 13–17 Years by State, NIS -Teen 2014

Females

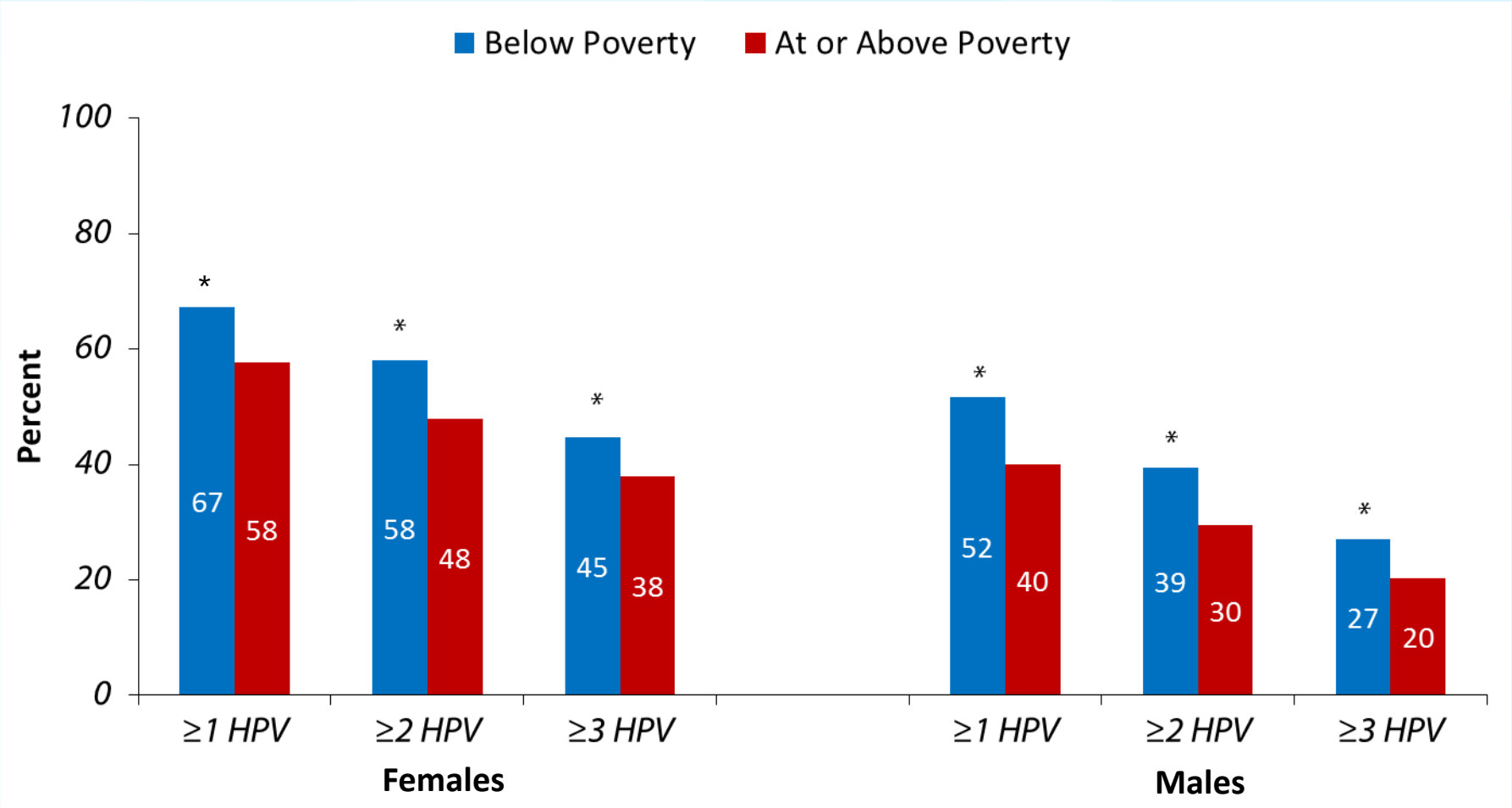


Males



NIS-Teen, National Immunization Survey - Teen
MMWR 2015;64:784-792

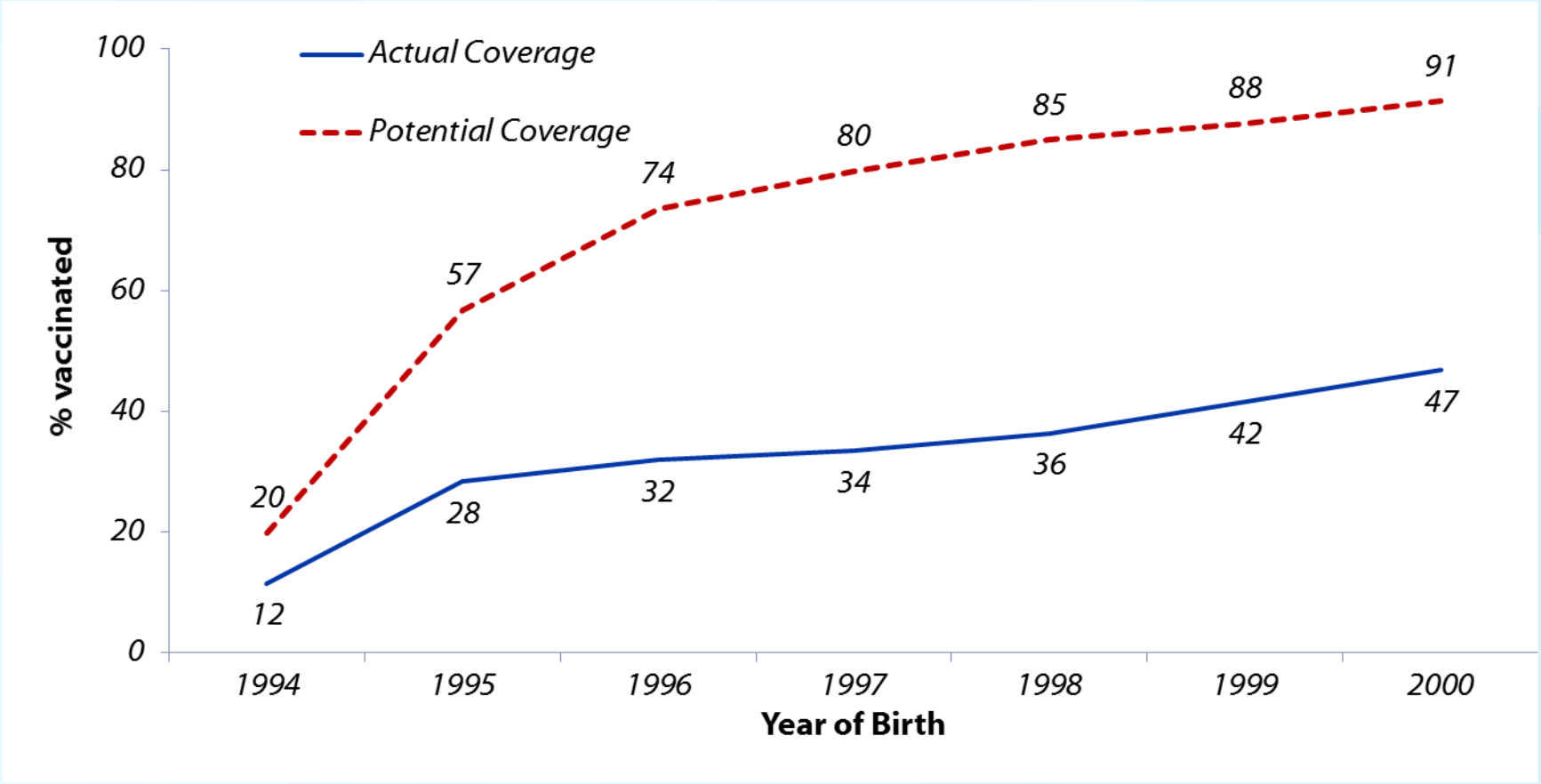
HPV Vaccination Coverage among Adolescents Aged 13-17 Years by Poverty Status NIS-Teen, United States, 2014



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

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

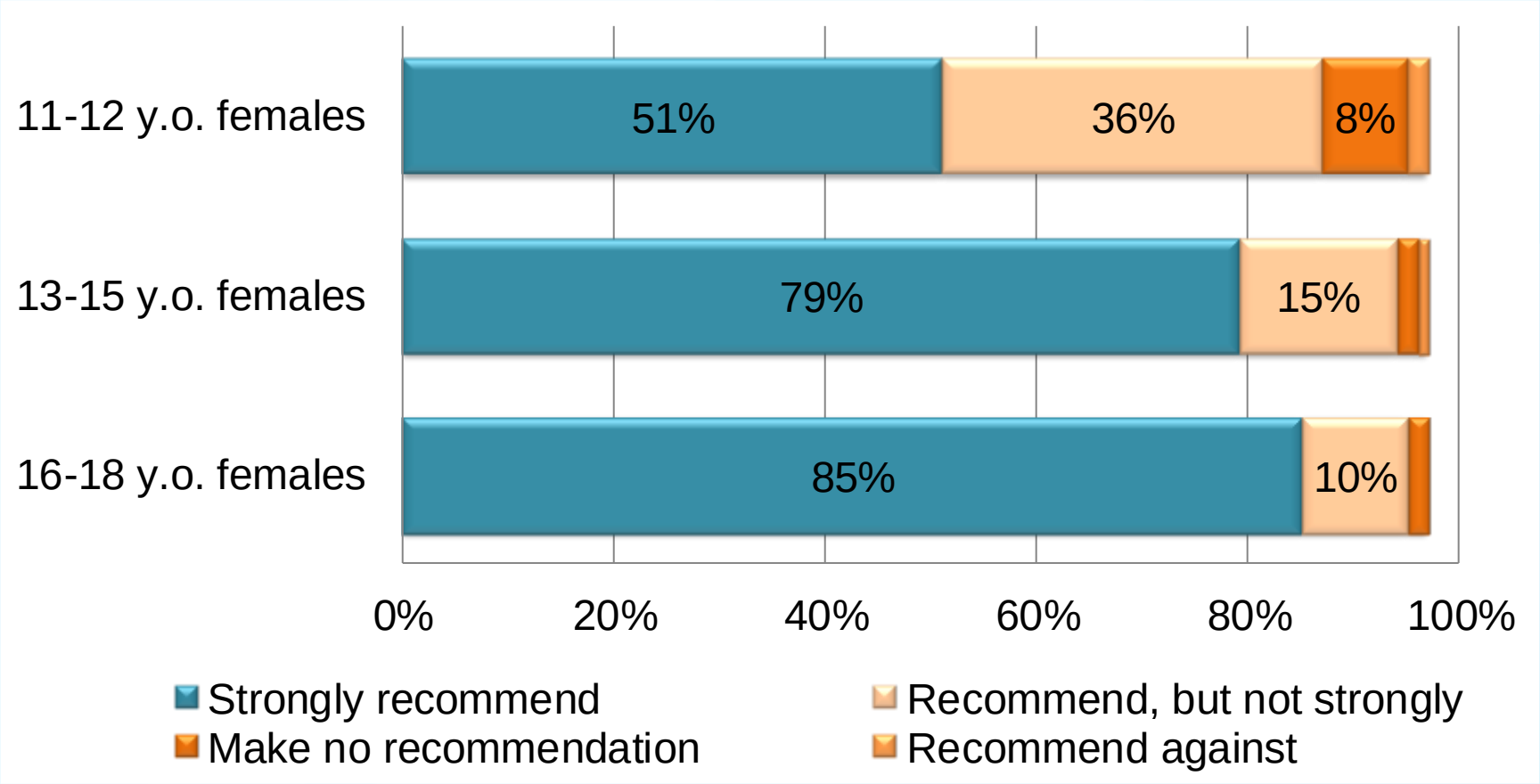
MMWR 2014;63:620-4

Top 5 reasons for not vaccinating daughter, among parents with no intention to vaccinate in the next 12 months, United States, 2013

Lack of knowledge	15.5%
Not needed or necessary	14.7%
Safety concern/side effects	14.2%
Not recommended by provider	13.0%
Not sexually active	11.3%

National Immunization Survey-Teen; MMWR 2014;63:620-4

Strength of Provider* HPV Vaccine Recommendation for Female Patients, (N=609)



Allison et al. Acad Pediatr 2013

*pediatricians and family physicians

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

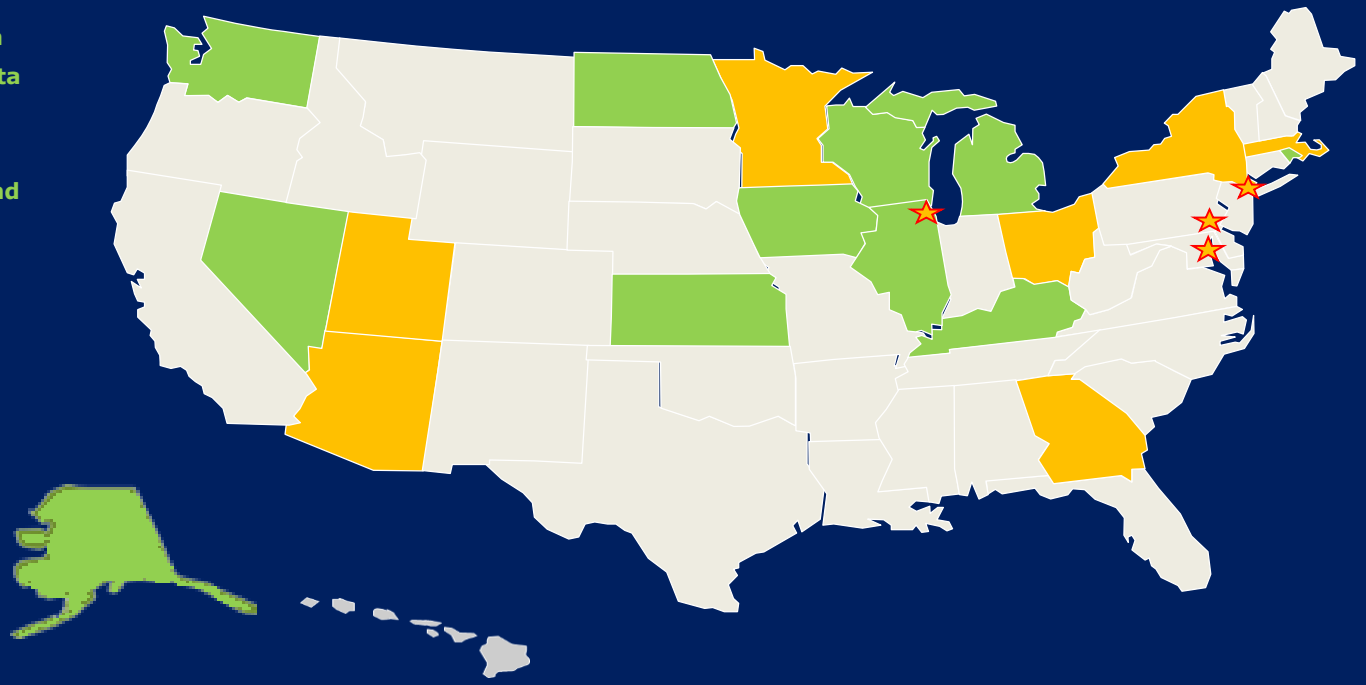
Strategies to Increase HPV Vaccination Coverage, United States

- 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

2014 Awardees

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



2013 Awardees

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

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

AFIX (Assessment, Feedback, Incentives, and eXchange)

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

- AFIX Home
- About AFIX +
- The Four Components
- Program Policies & Procedures Guide +
- Site Visit Questionnaire +
- Awardee Resources
- AFIX Quarterly Conference Calls
- Contacts +

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Related Links

Vaccines & Immunizations

Preteens and Teens Still Need

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.

More >

Contacts

Find your city/state/territory AFIX contacts to consult regarding specific AFIX questions.

Quick Vaccine Information Links

What's New!

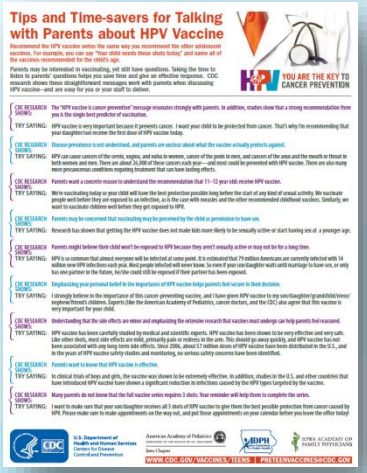
- Quarterly Conference Call Minutes
  March 26, 2015
- AFIX Policies and Procedures Guide
- AFIX Site Visit Questionnaire
- AFIX Site Visit Answer Guide

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



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

HPV Vaccine Key Points

POST-LICENSURE 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

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

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

† 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)[1]**
  - 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[2,3]
- **VSD conducted near-real time monitoring following 600,558 4vHPV doses (2011)[4]**
  - No associations with Guillain-Barré Syndrome, stroke, appendicitis, seizures, syncope, allergic reactions, and anaphylaxis
  - Non-significant elevated risk[5] (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[6]

[1] Slade et al, Postlicensure safety surveillance for quadrivalent human papillomavirus recombinant vaccine. JAMA 2009
[2] Stokley et al, Human Papillomavirus vaccination coverage among adolescent girls, 2007-12, and postlicensure vaccine safety monitoring 2006-2013 – United States. MMWR 2013
[3] Stokley et al, Human Papillomavirus vaccination coverage among adolescents 2007-13 and postlicensure vaccine safety monitoring 2006-2014 – United States. MMWR 2014
[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)
[6] Naleway et al, Absence of venous thromboembolism risk following quadrivalent human papillomavirus vaccination, Vaccine Safety Datalink, 2008-2011. Vaccine 2016

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)
  - Downloadable data files (Excel format) from VAERS website- 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

- **Souayah N et al. Guillain-Barré syndrome after Gardasil vaccination: data from Vaccine Adverse Event Reporting System 2006-2009.** Vaccine 2011;29:886-9
  - 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
  - CDC wrote a letter to the editor. http://www.ncbi.nlm.nih.gov/pubmed/21111783

- **Tomljenovic L, Shaw CA. Human papillomavirus (HPV) vaccine policy and evidence-based medicine: are they at odds?** Ann Med 2013;45:182-93
  - 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

[2]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 sucessess between program areas
Threats:
Lack of strong provider recommmendation
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

Acknowledgements

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Thank you

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For more information please contact Centers for Disease Control and Prevention

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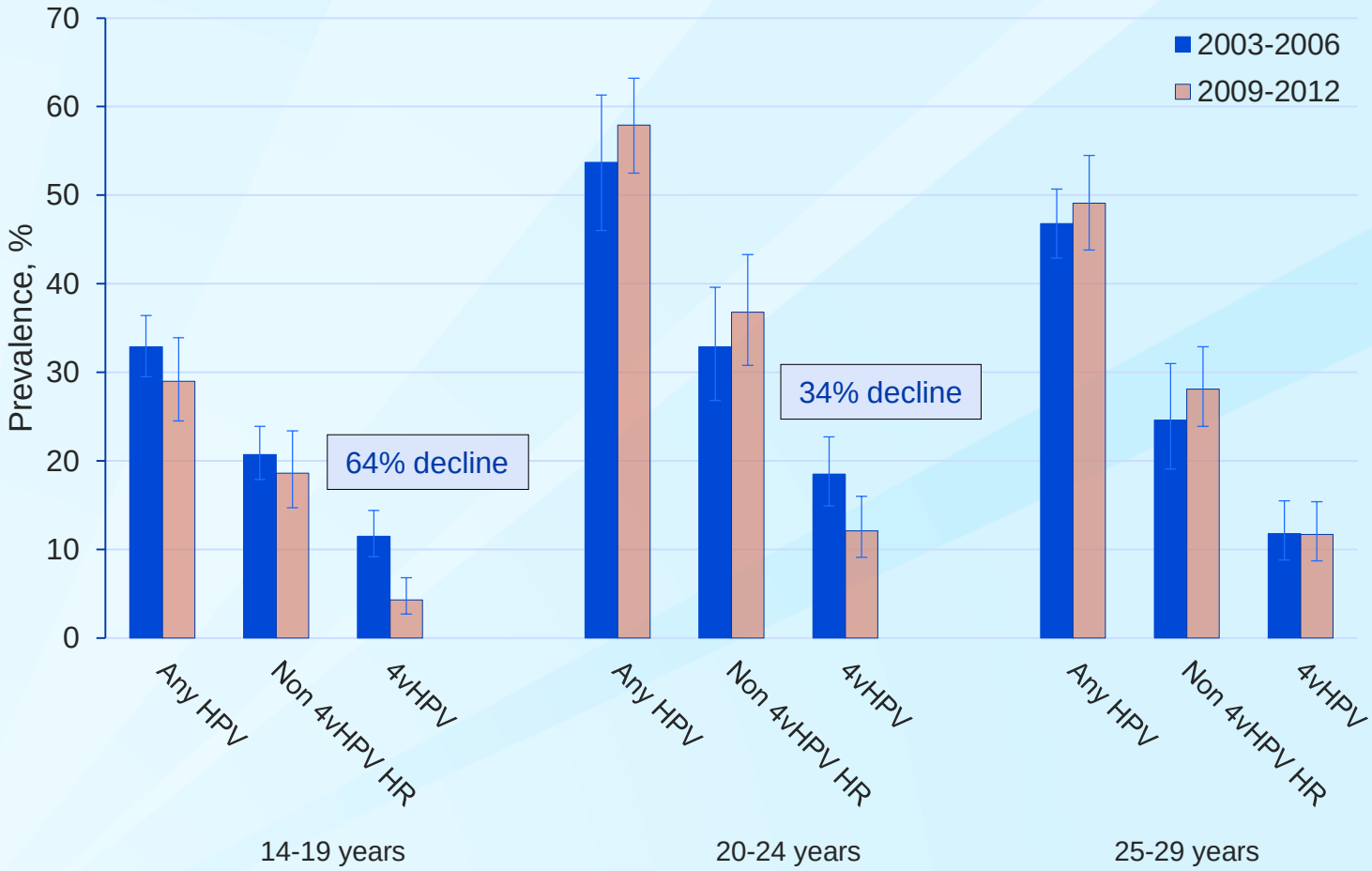
Telephone: 1-800-CDC-INFO (232-4636)/TTY: 1-888-232-6348

E-mail: cdcinfo@cdc.gov Web: http://www.cdc.gov

Prevalence of HPV in Cervicovaginal Swabs, by Age NHANES 2003-2006 and 2009-2012



Markowitz et al. Pediatrics 2016