

# HPV Vaccine Recommendation Update Webinar

**Centers for Disease Control and Prevention  
National Center for Immunization and Respiratory Diseases**  
Friday, April 3, 2015  
11:00AM-12:00PM EDT

# Presenters

- **Lauri E. Markowitz, MD**  
Centers for Disease Control and Prevention
- **Tom Shimabukuro, MD**  
Centers for Disease Control and Prevention

# Webinar Logistics

- **Audio:** All participant lines are muted.
- **Webinar Recording:** We are recording this webinar. We will notify all participants when the recording and presentation are available online.
- **Q&A Session:** Type your question into the “Questions” panel. We will read selected questions out loud for the presenters to answer.

# HPV Vaccination Update - 2015

Lauri E. Markowitz, MD  
Centers for Disease Control and Prevention

#PreteenVaxScene Webinar Series  
April 3, 2015

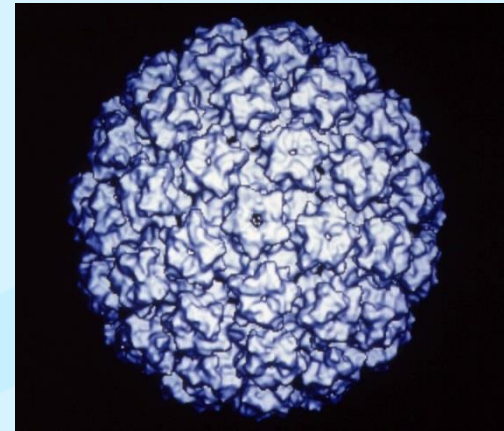
# Outline

- ❑ Overview of HPV vaccines
- ❑ HPV-associated cancers due to HPV types
- ❑ Data from 9-valent HPV vaccine trials
- ❑ Updated recommendations of the Advisory Committee on Immunization Practices

# Available prophylactic HPV vaccines

- ❑ Virus-like particle (VLP) vaccines
- ❑ The L1 major capsid protein expressed using recombinant technology
- ❑ L1 proteins self-assemble into VLPs
- ❑ Non infectious

HPV VLP



# Available HPV vaccines

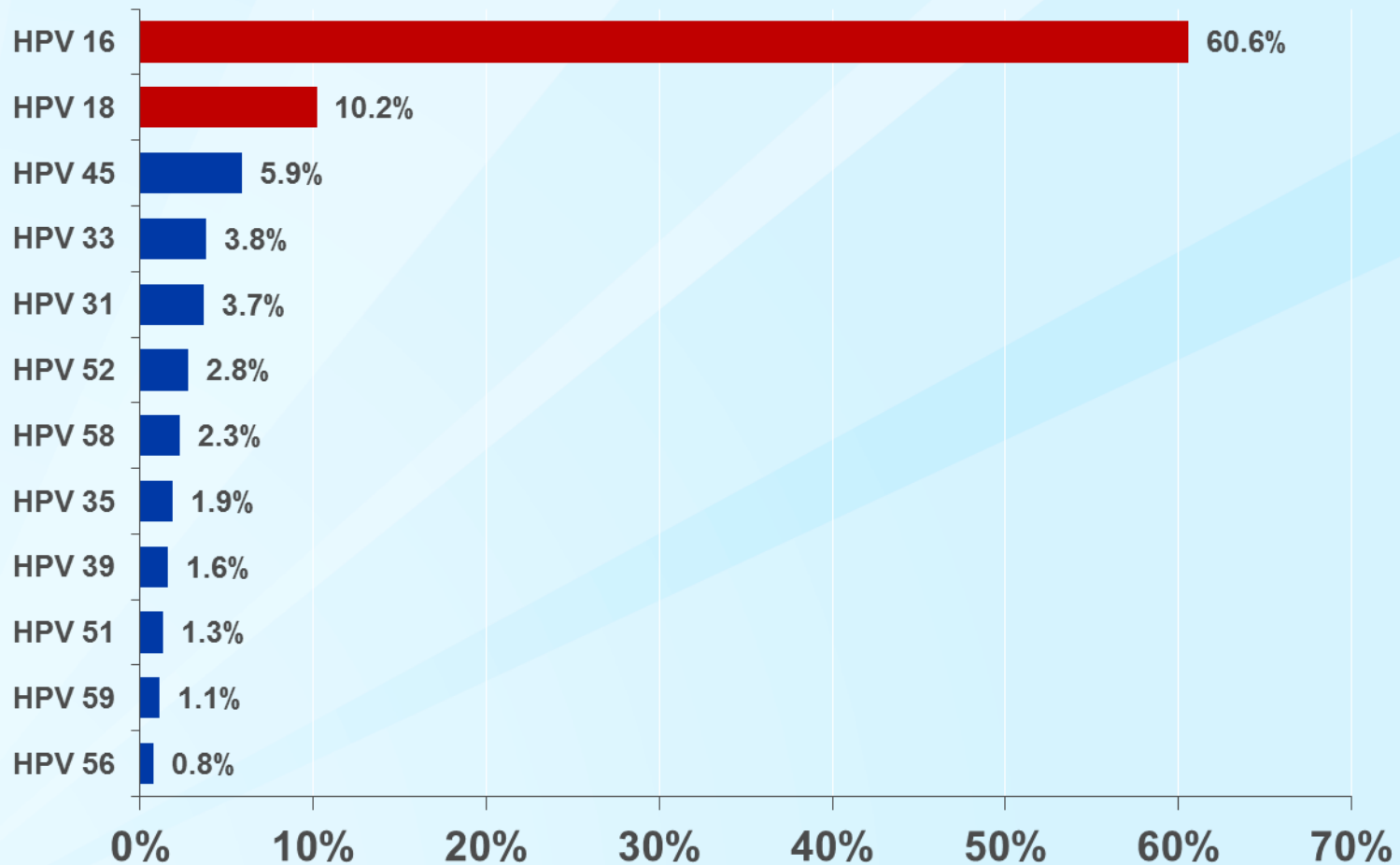
	<b>Bivalent 2vHPV (Cervarix)</b>	<b>Quadrivalent 4vHPV (Gardasil)</b>
<b>L1 VLP types</b>	<b>16, 18</b>	<b>6, 11, 16, 18</b>
<b>Manufacturer</b>	<b>GlaxoSmithKline</b>	<b>Merck</b>
<b>Adjuvant</b>	<b>AS04:</b> 500 µg aluminum hydroxide 50 µg 3- <i>O</i> -desacyl-4'- monophosphoryl lipid A	<b>AAHS:</b> 225 µg amorphous aluminum hydroxyphosphate sulfate

# Available HPV vaccines

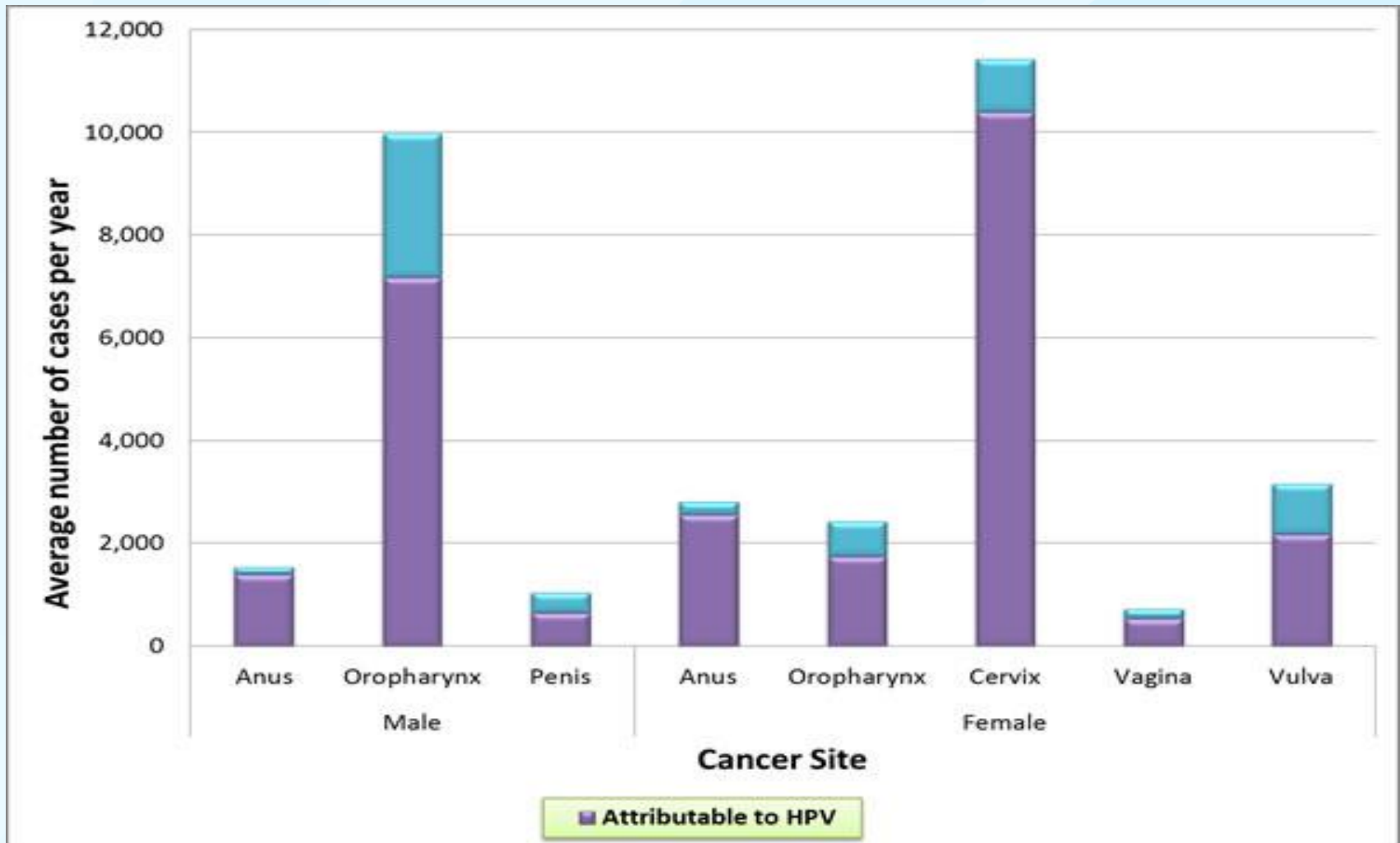
	<b>Bivalent 2vHPV (Cervarix)</b>	<b>Quadrivalent 4vHPV (Gardasil)</b>	<b>9-valent 9vHPV (Gardasil 9)</b>
<b>L1 VLP types</b>	<b>16, 18</b>	<b>6, 11, 16, 18</b>	<b>6, 11, 16, 18, 31, 33, 45, 52, 58</b>
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# Percentage of cervical cancers attributed to high risk HPV types, worldwide



# Estimated number of HPV-attributable cancer cases per year, United States



# Estimated percentages of cancers attributed to HPV in the U.S.

<b>Cancer</b>	<b>HPV attributable % (95% CI)</b>	<b>HPV 16/18 attributable % (95% CI)</b>	<b>HPV 31/33/45/52/58 attributable % (95% CI)</b>
Cervical	91 (88-92)	66 (63-69)	15 (12-17)
Vaginal	75 (63-84)	55 (43-67)	18 (11-30)
Vulvar	69 (62-75)	49 (41-56)	14 (10-20)
Penile	63 (52-73)	48 (37-59)	9 (4-17)
Anal			
Male	89 (77-95)	79 (66-88)	4 (1-13)
Female	92 (85-96)	80 (70-87)	11 (6-19)
Oropharyngeal			
Male	72 (68-76)	63 (59-68)	4 (3-7)
Female	63 (55-71)	51 (43-59)	9 (6-15)

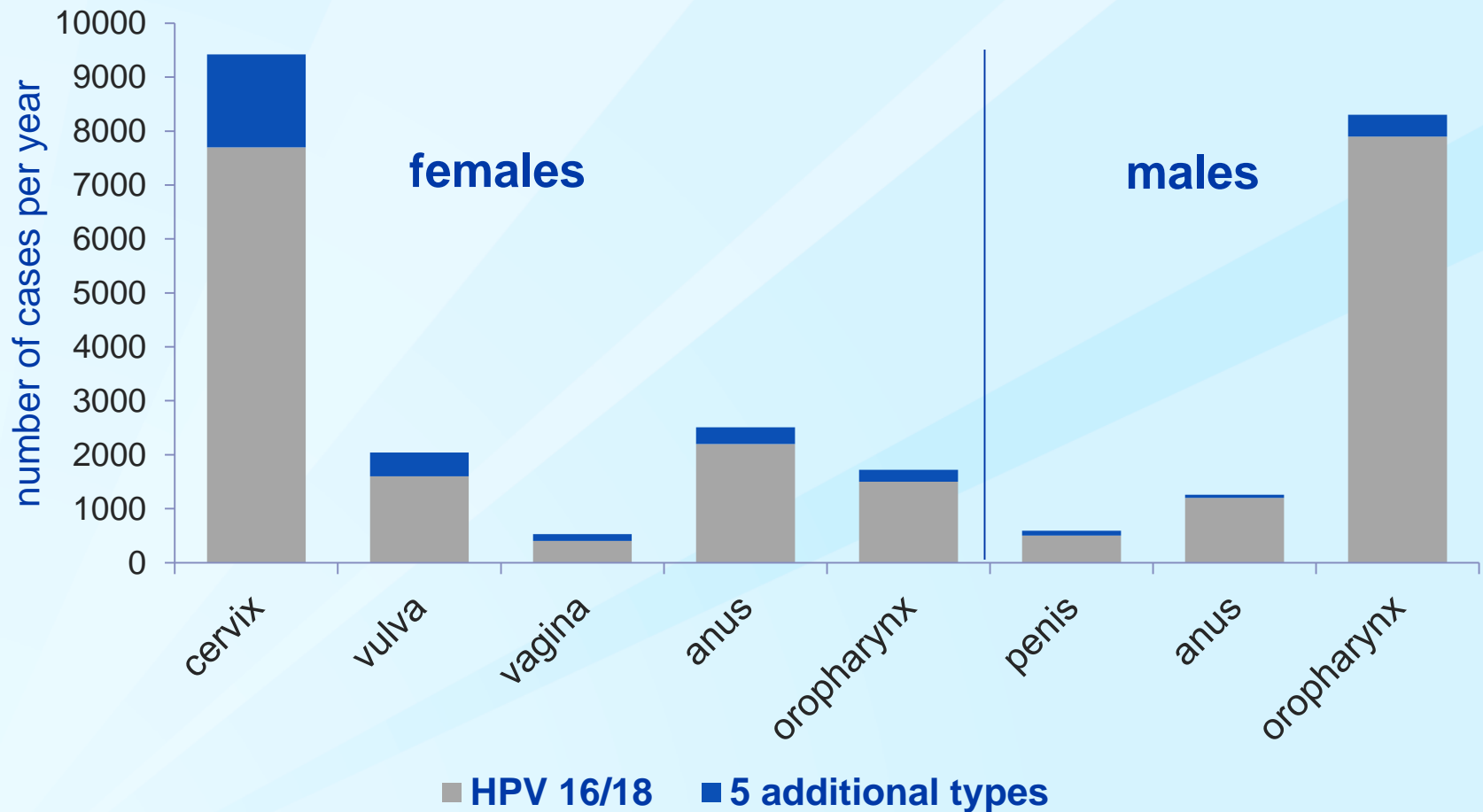
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## Estimated numbers of HPV-associated cancers attributable to HPV 16/18 and 5 additional types in 9-valent vaccine, U.S.\*



\*Based on years 2006-2010 <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6349a11.htm>  
and data from Saraiya, presented at AIN Conference, March 2015

# Summary: attribution of HPV 16/18 and HPV 31/33/45/52/58, United States

## □ HPV-associated cancers

- ~33,000 per year
- 64% of cancers attributable to HPV 16/18
  - 66% of cervical cancer
  - Other cancers: range, 48% penile -80% anal
- 10% of cancers attributable to additional 5 types
  - 15% of cervical cancer
  - Other cancers: range, 4% oropharyngeal -18% vaginal
  - Differences by sex: 14% for females; 4% for males

## □ ≥CIN2 lesions

- ~50% attributable to HPV 16/18
- ~25% attributable to 5 additional types

≥CIN, cervical intraepithelial neoplasia grade 2 or worse  
% among all HPV-associated cancers

# 9-valent HPV vaccine

- ❑ **Licensed by FDA in December 2014**
- ❑ **Clinical development program**
  - Efficacy trial
  - Immunogenicity/immunobridging trials
  - Concomitant use trials



# 9-valent HPV vaccine efficacy trial

## □ Design

- ~14,000 women aged 16-26 years
- Randomized trial: 9vHPV or 4vHPV

## □ Objectives

- Demonstrate efficacy for HPV 31,33,45,52,58
- Demonstrate non-inferior immunogenicity for HPV 6,11,16,18

## 9-valent HPV vaccine efficacy trial per protocol population results

HPV 31,33,45,52,58 related outcomes	9vHPV n/total	4vHPV n/total	Vaccine efficacy (95% CI)
≥CIN2, VIN2/3, VaIN2/3	1/6016	30/6017	96.7 (80.9, 99.8)
6 month persistent infection	35/5939	810/5953	96.0 (94.4, 97.2)

- High efficacy against HPV 31,33,45,52,58 outcomes

≥CIN2 = cervical intraepithelial neoplasia grade 2 or 3, or adenocarcinoma in situ; VIN = vulvar intraepithelial neoplasia; VaIN = vaginal intraepithelial neoplasia

# 9-valent HPV vaccine efficacy trial

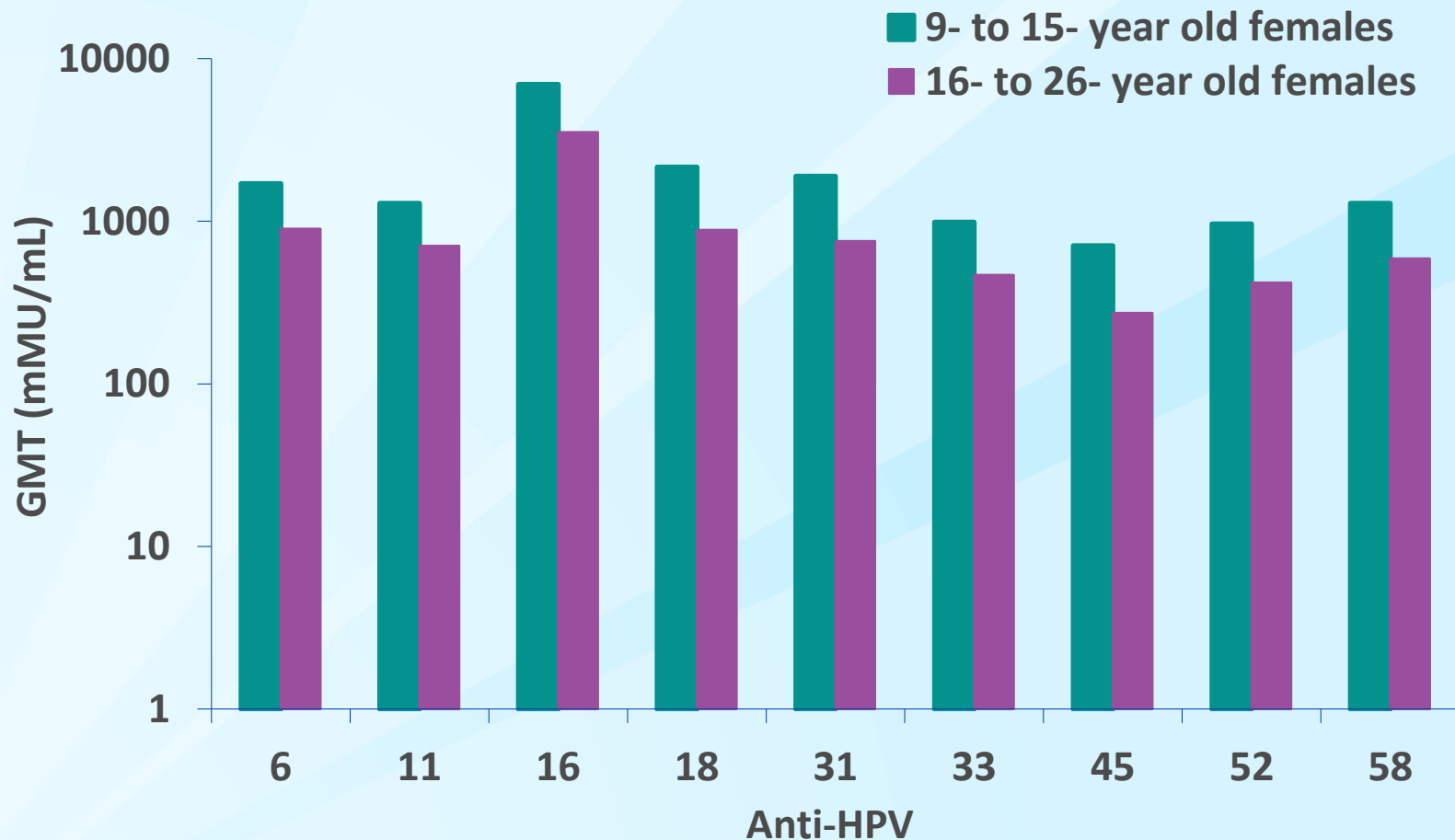
## per protocol population results

HPV 6,11,16,18 related outcomes	9vHPV n/total	4vHPV n/total
≥CIN2, VIN2/3, VaIN2/3	1/5883	3/5898

- Few high grade outcomes due to HPV 6,11,16,18
- Non-inferiority immunogenicity for HPV 6,11,16,18
  - ≥99% seroconversion; GMTs non-inferior

≥CIN2 = cervical intraepithelial neoplasia grade 2 or 3, or adenocarcinoma in situ; VIN = vulvar intraepithelial neoplasia; VaIN = vaginal intraepithelial neoplasia

# 9-valent HPV vaccine adult-to-adolescent immunobridging trial



Data from per protocol population; Antibody measured by cLIA at month 7

# 9-valent HPV vaccine trials

## ❑ Efficacy

- ~97% protection against HPV 31,33,45,52,58-related outcomes
- Similar protection against HPV 6,11,16,18-related disease

## ❑ Non-inferior immunogenicity

- For HPV 6,11,16,18 compared with 4vHPV in 16–26 and 9–15 year olds
- For all 9 HPV vaccine types in adolescent females and males compared to adult females and in adult males compared to adult females

## ❑ Concomitant use

- No impact on immunogenicity or safety administered concomitantly with quadrivalent meningococcal conjugate vaccine (Menactra) and tetanus, diphtheria, acellular pertussis vaccine (Adacel)

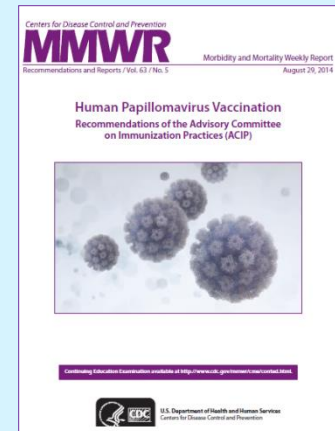
# 9-valent HPV vaccine safety

- ❑ **Trials included >15,000 9vHPV vaccinees**
- ❑ **Generally well tolerated; safety profile similar to 4vHPV**
  - 9vHPV - more injection-site reactions
    - swelling (40.3% vs 29.1% )
    - erythema (34.0% vs 25.8%)
  - Injection-site erythema and swelling increased with number of doses
- ❑ **Concomitant use**
  - No difference in safety profile when co-administered with quadrivalent meningococcal conjugate vaccine (Menactra) and tetanus, diphtheria, acellular pertussis vaccine (Adacel)

# **RECOMMENDATIONS**

# Recommendations for HPV vaccination in the United States (before February 2015)

- ❑ Routine vaccination at age 11 or 12 years\*
- ❑ Vaccination recommended through age 26 for females and through age 21 for males not previously vaccinated
- ❑ Vaccination recommended for immunocompromised persons (including persons HIV-infected) and for men who have sex with men through age 26
- ❑ 3-dose schedule (0,1-2 and 6 months)
- ❑ Vaccines
  - 2vHPV or 4vHPV for females
  - 4vHPV for males



\*vaccination series can be started at age 9 years



## Available HPV vaccines

	<b>Bivalent (Cervarix)</b>	<b>Quadrivalent (Gardasil)</b>	<b>9-Valent (Gardasil 9)</b>
Licensed for	Females 9-25 years	Females 9-26 years Males 9-26 years	Females 9-26 years Males 9-15 years

- At the time of the first application to FDA, 9vHPV trials in males 16-26 years had not been completed
- Immunogenicity data now are available for males 16-26 years, reviewed by ACIP and submitted to FDA
- ACIP recommended use of 9vHPV in the currently recommended age groups

# Updated ACIP recommendations

- ❑ Routine vaccination at age 11 or 12 years\*
- ❑ Vaccination recommended through age 26 for females and through age 21 for males not previously vaccinated
- ❑ Vaccination recommended for men who have sex with men and immunocompromised men (including persons HIV-infected) through age 26
- ❑ 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

\*vaccination series can be started at 9 years of age

## Updated ACIP recommendations

2vHPV, 4vHPV and 9vHPV all protect against HPV 16 and 18, types that cause about 66% of cervical cancers and the majority of other HPV-attributable cancers in the United States. 9vHPV targets five additional cancer causing types, which account for about 15% of cervical cancers. 4vHPV and 9vHPV also protect against HPV 6 and 11, types that cause genital warts.

## **Updated ACIP recommendations: Interchangeability**

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

# Updated ACIP recommendations: 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
- ❑ If the vaccine schedule is interrupted, the vaccination series does not need to be restarted

# Updated ACIP recommendations: HPV vaccination during pregnancy

- ❑ No change in recommendations
- ❑ HPV vaccine not recommended for use in pregnancy

A new vaccine in pregnancy registry has been established for 9vHPV. Registries for 4vHPV and 2vHPV have been closed with concurrence from FDA.

4vHPV registry closed in 2012

2vHPV registry closed in 2015 <http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm434787.htm>

## **9vHPV vaccination for persons who completed a HPV vaccination series**

- ❑ The manufacturer did not seek an indication for 9vHPV vaccination for persons who previously completed a HPV vaccination series
- ❑ A study of 9vHPV in prior 4vHPV vaccinees was conducted
- ❑ Due time limitations (abbreviated ACIP meeting), this was not discussed; will be discussed at a future ACIP meeting

## Summary: 9-valent HPV vaccine

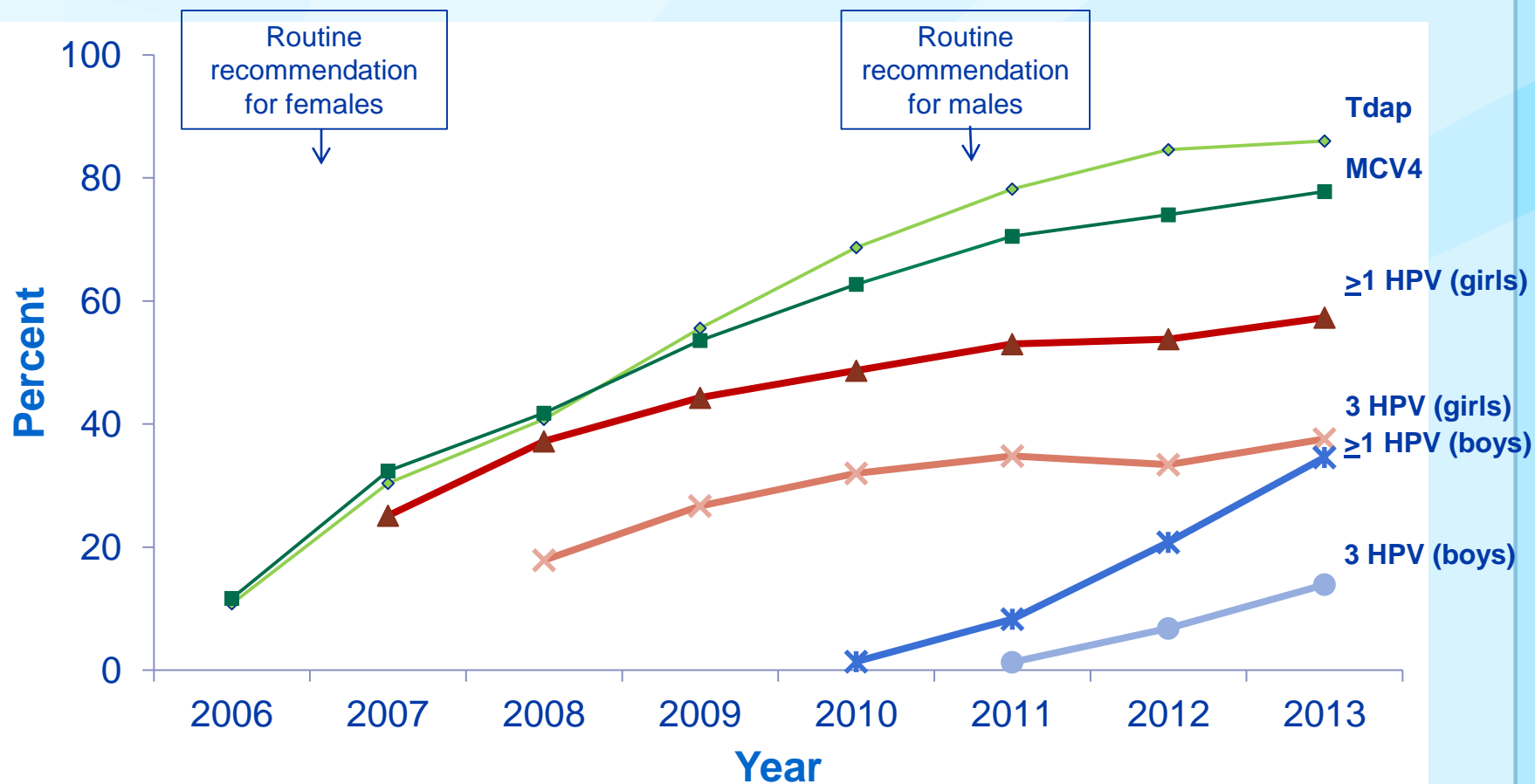
- ❑ Licensed by FDA in December 2014
- ❑ Recommended by ACIP in February 2015
- ❑ One of 3 HPV vaccines that can be used for routine vaccination of females and one of 2 for males
- ❑ Targets 5 additional high risk types
  - Overall 14% of HPV-associated cancers in females; 4% in males attributable to these 5 types
  - 15% of cervical cancers attributable to these 5 types



## Next steps

- ❑ 9vHPV available from manufacturer starting in February 2015
- ❑ CDC awarded a Vaccines for Children (VFC) contract for 9vHPV
- ❑ Efforts need to continue to increase HPV vaccination coverage

# National estimated vaccination coverage levels among adolescents 13-17 years NIS-Teen, 2006-2013



NIS-Teen = National Immunization Survey-Teen  
MMWR 2014;63:625-33

## Resources

ACIP website with slides, minutes and recommendations

<http://www.cdc.gov/vaccines/acip/index.html>

Additional resources for providers/patients/clients

<http://www.cdc.gov/vaccines/vpd-vac/hpv/>

[www.cdc.gov/vaccines/YouAreTheKey](http://www.cdc.gov/vaccines/YouAreTheKey)

[www.cdc.gov/hpv](http://www.cdc.gov/hpv)[www.cdc.gov/vaccines/teens](http://www.cdc.gov/vaccines/teens)

# Thank you

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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.

# Human Papillomavirus (HPV) Vaccine Safety Update

**Tom Shimabukuro, MD**

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April 3, 2015

# Disclaimer

**The findings in this presentation are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention**

**Disclosure: No conflicts of interest**

## Outline

- **Update of HPV vaccine safety monitoring and publications\***
- **Ongoing HPV vaccine safety-related activities**
- **9-valent HPV (9vHPV) vaccine safety monitoring plans**

\* Predominately quadrivalent human papillomavirus vaccine (4vHPV)

# CDC Immunization Safety Office Post-licensure Vaccine Safety Monitoring Infrastructure

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 ~9.4 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



# Postlicensure HPV Vaccine Safety Publications: General Safety

- **VAERS Postlicensure safety summary**
  - Initial review in 2009<sup>1</sup>--Proportion of reports for venous thromboembolism (VTE) and syncope after 4vHPV were higher than expected
  - No other signals identified through passive surveillance
  - Updated reviews in 2013 and 2014--no new concerns identified<sup>2,3</sup>
- **VSD Rapid Cycle Analysis (RCA) conducted near-real time monitoring following 600,558 4vHPV doses (2011)<sup>4</sup>**
  - No statistically significant associations with Guillain-Barré Syndrome, stroke, VTE, appendicitis, seizures, syncope, allergic reactions, and anaphylaxis
  - Non-significant elevated risk (RR=1.98) for VTE in females 9-17 years
- **General safety assessment from two large US health plans with 189,629 female vaccinees (2012)<sup>5</sup>**
  - 4vHPV associated with syncope and skin infections in the two weeks following immunization

<sup>1</sup> Slade et al, Post-licensure safety surveillance for quadrivalent human papillomavirus recombinant vaccine. JAMA 2009

<sup>2</sup> Stokely et al, HPV vaccination coverage among adolescents 2007-12 and post-licensure vaccine safety monitoring 2006-13. MMWR 2013

<sup>3</sup> Stokely et al, HPV vaccination coverage among adolescents 2007-13 and post-licensure vaccine safety monitoring 2006-14. MMWR 2014

<sup>4</sup> Gee et al, Monitoring the safety of quadrivalent human papillomavirus vaccine: findings from the VSD. Vaccine 2011

<sup>5</sup> Klein et al, Safety of quadrivalent human papillomavirus vaccine administered routinely to females, Arch Ped Adolesc Med 2012

## HPV vaccine and Venous Thromboembolism (VTE)

- **Possible association found in VAERS and VSD RCA studies<sup>1, 2</sup>**
  - VAERS: Proportion of reports were higher than expected
  - VSD RCA: Elevated non-significant risk identified among females ages 9-17 years
- **Two national register-based cohort studies found no elevated risk for VTE following 4vHPV:**
  - 296,826 vaccinated females aged 10-17 years (Denmark and Sweden)<sup>3</sup>
  - 500,345 vaccinated females aged 10-44 years (Denmark)<sup>4</sup>
- **Preliminary VSD study results using self-controlled case series method found no increased risk of VTE following 4vHPV among persons aged 9-26 years<sup>5</sup>**

<sup>1</sup> Slade et al, Post-licensure safety surveillance for quadrivalent human papillomavirus recombinant vaccine. JAMA 2009

<sup>2</sup> Gee et al, Monitoring the safety of 4vHPV: findings from the VSD. Vaccine 2011

<sup>3</sup> Arnheim-Dahlstrom et al, Autoimmune, neurological, and venous thromboembolic adverse events following immunization of adolescent girls with 4vHPV4 in Denmark and Sweden. BMJ 2013

<sup>4</sup> Scheller et al, 4vHPV and the risk of venous thromboembolism. JAMA 2014

<sup>5</sup> Naleway A et al, Abstract presented at International Papillomavirus Conference, 2014

## Postlicensure HPV Vaccine Safety Publications: Autoimmune and Neurologic Diseases

- **No evidence for causal association observed between 4vHPV and autoimmune and/or neurologic conditions**
  - 16 autoimmune conditions at two health plans among 189, 629 vaccinated females aged 9-26 years (US)<sup>1</sup>
  - 23 autoimmune, 5 neurologic conditions and VTE among 296,826 vaccinated females aged 10-17 years (Denmark and Sweden)<sup>2</sup>
  - 6 autoimmune outcomes among 1,365 (269 cases, 1,096 controls) 14-27 year olds (France)<sup>3</sup>
  - Multiple sclerosis and demyelinating diseases among 789,082 vaccinated females aged 10-44 years (Denmark)<sup>4</sup>

<sup>1</sup>Chao C et al, Surveillance of autoimmune conditions following routine use of quadrivalent human papillomavirus vaccine. J Intern Med 2012

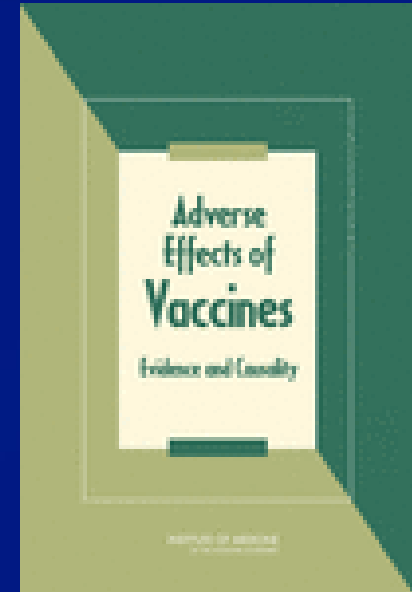
<sup>2</sup>Arnheim-Dahlstrom et al, Autoimmune, neurological, and venous thromboembolic adverse events following immunization of adolescent girls with HPV4 in Denmark and Sweden. BMJ 2013

<sup>3</sup>Grimaldi-Bensouda L et al, Autoimmune disorders and quadrivalent human papillomavirus vaccination of young female subjects. J Intern Med 2013

<sup>4</sup>Scheller NM et al, Quadrivalent HPV vaccination and the risk of multiple sclerosis and other demyelinating diseases of the central nervous system. JAMA 2015

# 2011 Institute of Medicine (IOM) Report on Adverse Effects of Vaccines

- **Syncope following vaccination**
  - IOM concluded that, “*the injection of a vaccine was a contributing cause of syncope.*”
- **Anaphylaxis following vaccination**
  - IOM concluded that, “*the evidence favors acceptance of a causal relationship between HPV vaccine and anaphylaxis.*”



## **CDC's Immunization Safety Office: Current HPV Vaccine Safety-Related Activities**

- **VAERS:**
  - Ongoing monitoring of US reports (2vHPV and 4vHPV)
  - Clinical review of deaths (and other pre-specified adverse outcomes as needed)
  - FDA data mining
- **CISA:**
  - Assessing feasibility and impact of implementing an oral water hydration strategy to prevent post-vaccination presyncope and syncope in adolescents and young adults receiving any intramuscular vaccines (including HPV vaccine)
    - Interventional clinical trial registered at [Clinical.Trials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02353390) (NCT02353390)

## **CDC's Immunization Safety Office: HPV Vaccine Safety-Related Activities**

- **VSD:**
  - Addressing HPV vaccine safety in special populations:
    - Safety of 4vHPV among males
    - Inadvertent 4vHPV vaccination during pregnancy
  - Addressing HPV vaccine safety concerns from case reports and/or media:
    - Autoimmune disease risk following 4vHPV
    - Premature ovarian insufficiency following 4vHPV
    - Mortality following 4vHPV and other adolescent vaccines

# 9vHPV Vaccine Safety

- **7 prelicensure studies**
- **Generally well tolerated in > 15,000 subjects**
  - Adverse event profile similar to that of 4vHPV across age, gender, race, and ethnicity
  - More injection site-related swelling and erythema in 9vHPV group
  - Among inadvertent pregnancies occurring during clinical studies:<sup>1,2</sup>
    - The proportion of adverse outcomes observed were consistent with pregnancy outcomes observed in the general population
    - In sub-analyses, pregnancies within 30 days of 9vHPV vaccination resulted in spontaneous abortion more frequently than after 4vHPV:
      - 9vHPV group 27.4% (17/62) vs. 4vHPV group 12.7% (7/55)
      - Spontaneous abortion background rate: 31%<sup>3</sup>

<sup>1</sup> 9vHPV is FDA Category B for pregnancy, <http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM426457.pdf>

<sup>2</sup> <https://clinicaltrials.gov/ct2/show/NCT01651949?term=v503&rank=3>

<sup>3</sup> Wilcox A et al. Incidence of early loss of pregnancy. NEJM 1988

# 9vHPV Vaccine Safety Monitoring and Evaluation: CDC

- **VAERS:**
  - Monitor reports using automated data
  - Clinical review of deaths (and other pre-specified adverse outcomes as needed)
  - FDA data mining
- **VSD:**
  - Near real-time monitoring for several pre-specified outcomes through Rapid Cycle Analysis
  - Evaluation of spontaneous abortion following 9vHPV
    - Label indicates possible increase relative to 4vHPV



# 9vHPV Vaccine Safety Monitoring and Evaluation: Manufacturer and FDA

- **Postmarketing commitments by manufacturer:<sup>1</sup>**
  - Completion of two 10-year study extensions evaluating the long-term safety, immunogenicity, and effectiveness in:
    - males and females 9-15 years
    - females 16-26 years
  - Observational study to further characterize the safety profile in approximately 10,000 persons
  - Pregnancy registry to prospectively collect data on spontaneously reported exposures occurring within 30 days prior to the last menstrual period or any time during pregnancy
- **FDA's Sentinel Initiative pharmacovigilance plan:<sup>2</sup>**
  - General safety study
  - Pregnancy outcomes study

<sup>1</sup><http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm426520.htm>

<sup>2</sup><http://www.brookings.edu/~media/events/2015/02/05%20fda%20sentinel%20initiative%20workshop/2015%20sentinel%20initiative%20annual%20meeting%20slide%20deck.pdf>

## Conclusion

- **4vHPV has a good safety profile as demonstrated by:**
  - VAERS and VSD safety monitoring data
  - Published and preliminary data from many sources
- **Safety monitoring and evaluation continue for all HPV vaccines**

**Thank you!**



# Thank you for participating!

For more information, visit  
[www.cdc.gov/vaccines/teens](http://www.cdc.gov/vaccines/teens)