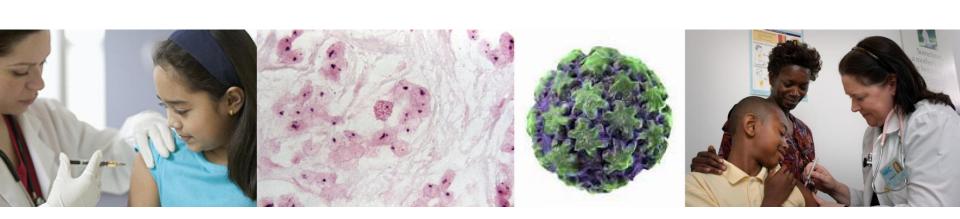
# Public Health Importance of Human Papillomavirus Infection and Disease



#### Mona Saraiya, MD MPH

Associate Director for Global Cancer

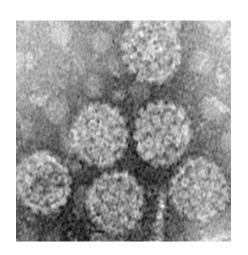
Division of Cancer Prevention and Control

National Center for Chronic Disease Prevention and Health Promotion

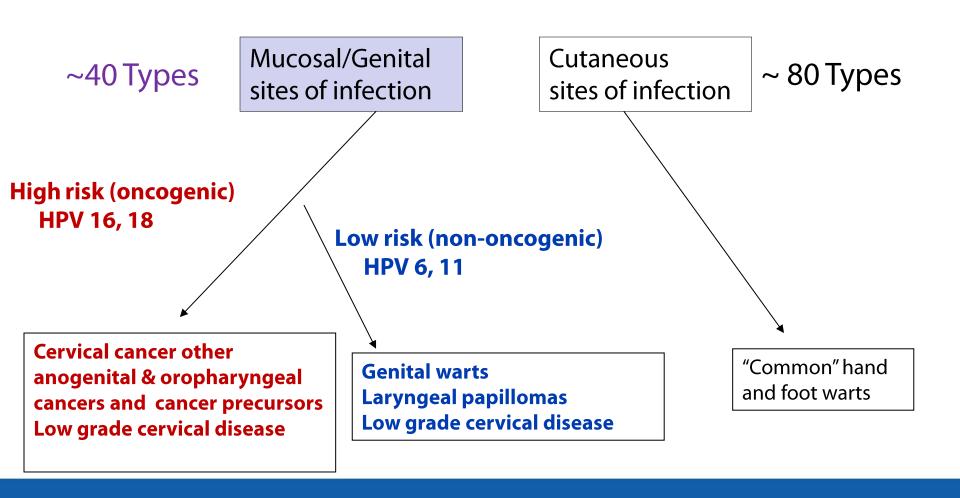


### **Human Papillomaviruses**

- Double-stranded DNA virus
  - More than 120 closely related viruses
    - Types numbered in order of discovery
- HPV infection confined to epithelium
  - Begins in base of epithelium, cells proliferate and are not killed
- Humoral and cellular immune responses identified
  - Antibodies detected in less than 70% of females infected



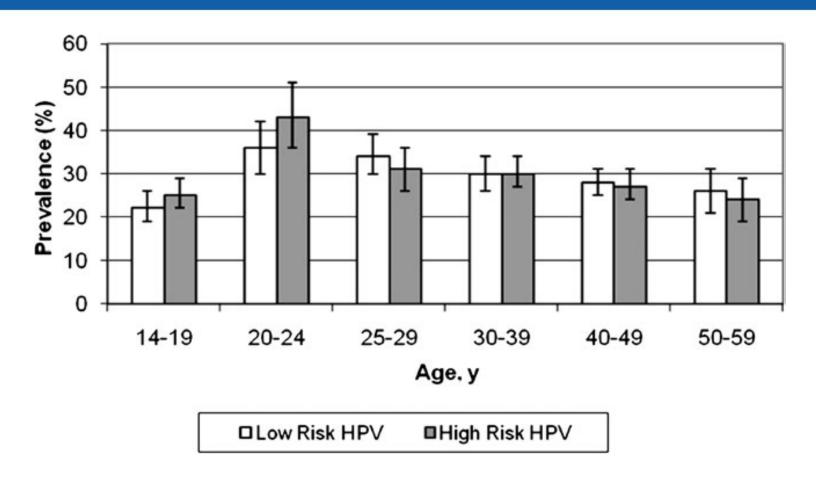
### **HPV Types Differ in their Disease Associations**



## Overview of HPV Epidemiology and Natural History

- HPV infection is very prevalent in the population
  - Almost all sexually active persons will acquire HPV
  - > In the US:
    - ~79 million infected
    - 14 million new infections per year
- Genital HPV is first acquired soon after onset of sexual activity
  - > 40% infected within 2 years
- Infection is usually transient, asymptomatic
- Cancer is a rare outcome
  - Requires persistent infection with high risk HPV types

## Weighted Prevalence of HPV in US Women (14-59 years) – NHANES 2003-2006



### Burden of Disease Caused by Low-Risk HPV

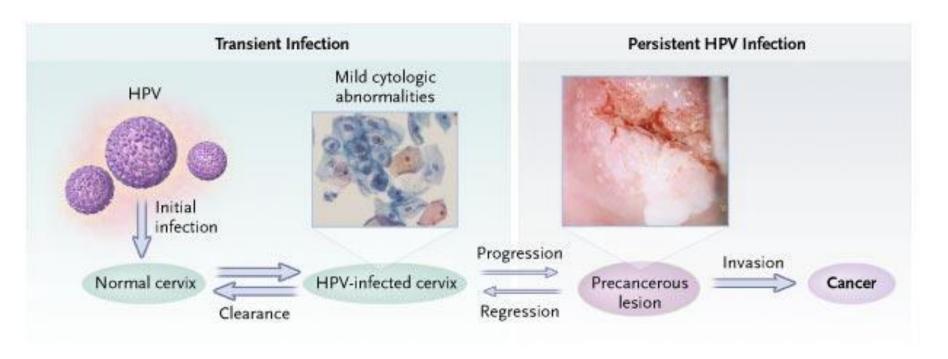
#### Genital Warts

- Over 300,000 new cases a year in the US
- Peak incidence in persons aged 20-29 years
- Recur 40% of the time and lead to repeat clinical visits, treatments and psychosocial stigma

#### ■ Recurrent respiratory papillomatosis (RRP)

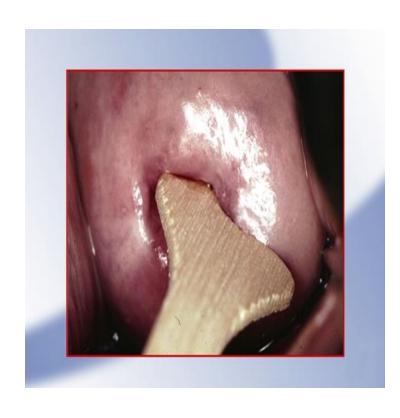
- Rare condition in which warts grow in the throat
- Occur in children (juvenile-onset) and adults (adult-onset)
- Can result in airway obstruction requiring multiple surgeries

### **HPV: Natural History of Cervical Infection**



- Persistent infection with high-risk types required for progression to precancer and cancer
- □ Peak incidence of precancers in late 20's and of cancers in mid to late 40's

## **Cervical Cancer Screening Pap (Papanicolaou) Test**



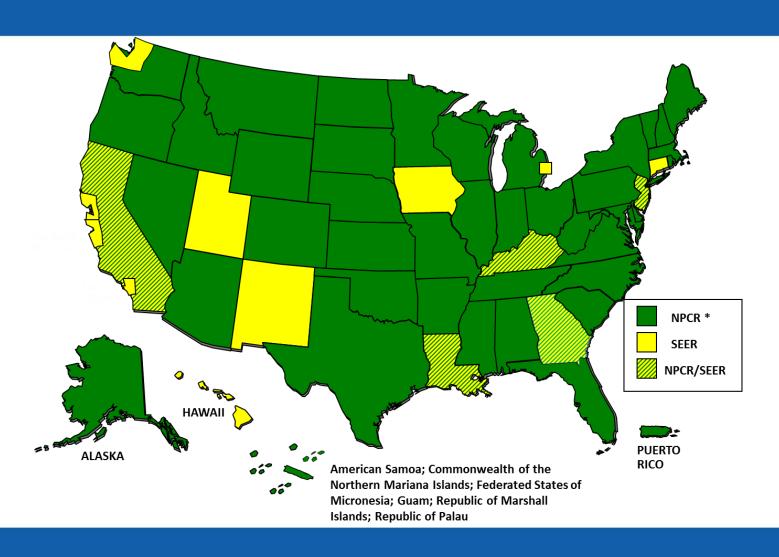
- A test which collects cells from the surface of the cervix and looks for abnormal cells
- Precancer can be detected and treated before cervical cancer develops
- HPV testing added as part of screening, resulting in improved sensitivity while safely allowing for extension of screening intervals

### New Cervical Cancer Screening Guidelines: ACS, USPSTF, ACOG

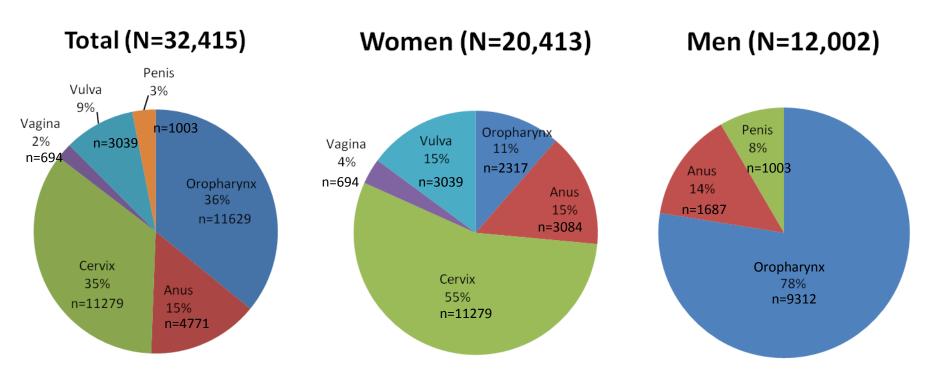
	ACS 2012	USPSTF 2012	ACOG 2012
Age to start	Age 21 years	Age 21 years	Age 21 years
Women ages 21-29 years	Pap every 3 years	Pap every 3 years	Pap every 3 years
Women ages 30-65 years	Cotesting every 5 years (preferred) or Every 3 years with Pap alone	Or Every 3 years with Pap alone	Cotesting every 5 years (preferred) or Every 3 years with Pap alone
Screening among fully vaccinated		Not reviewed	Same as for non-vaccinated

<sup>\*</sup>All guidelines recommend that women who have been adequately screened can discontinue Pap at age 65.

### Federally Funded Cancer Registries, 2013



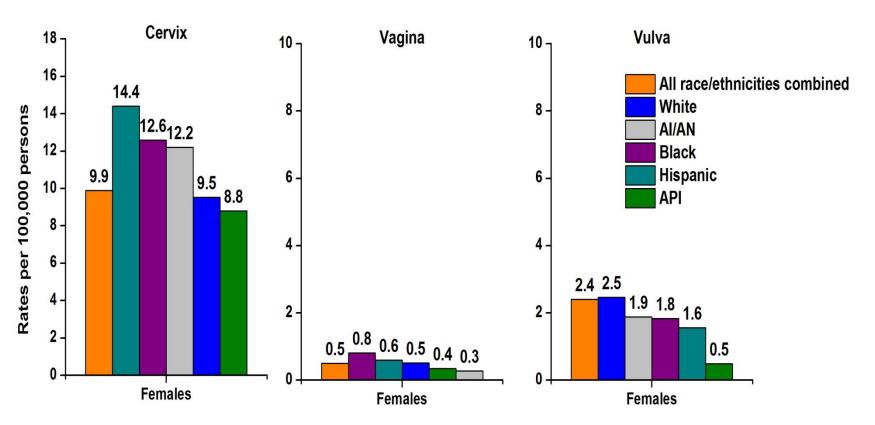
## Average Number of New HPV-associated Cancers Overall, and by Sex, in the United States, 2005-2009



Jemal A et al. J Natl Cancer Inst 2013;105:175-201

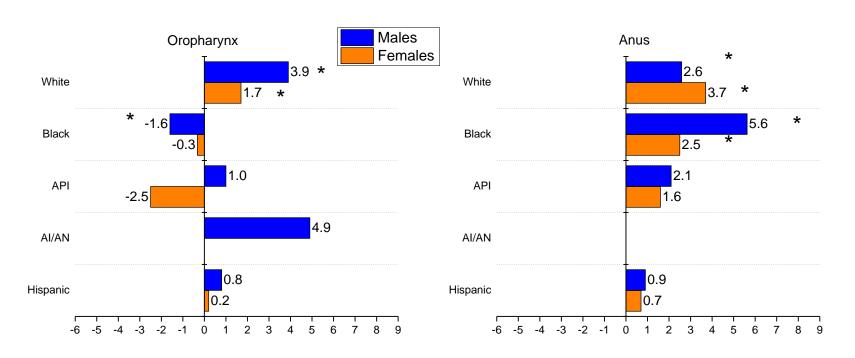
\*In addition: Cervical disease and pre-invasive cancers: CIN1,2,3~ 1.4 million; AIN3~4300; VIN3~27,000, VAIN3~7600 (CDC, unpublished data)

## Cervical, Vaginal and Vulvar Cancers in the United States by Race and Ethnicity, 2005–2009



Y axis scale is different for cervical cancer.

## Trends in Oropharyngeal and Anal Cancer by Sex, Race, and Ethnicity in the United States, 2000–2009

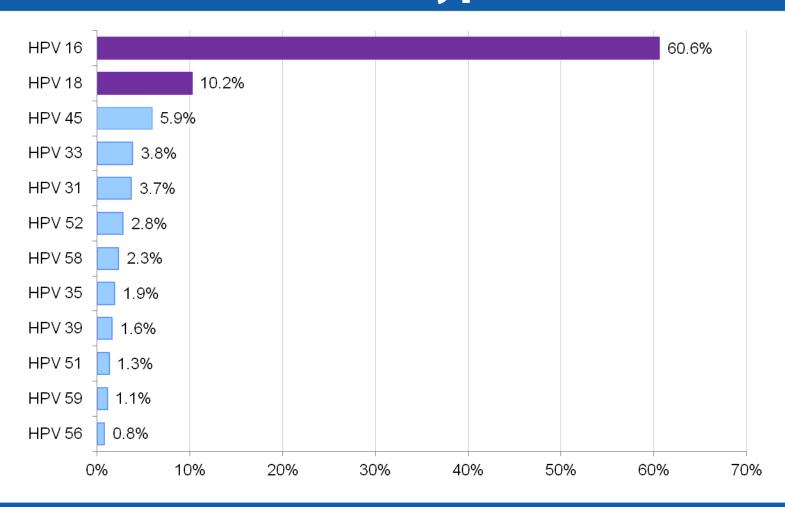


Average Annual Percent Change

Average Annual Percent Change

<sup>\*</sup>statistically significantly different from zero at P<0.05

### Percentage of Cervical Cancers Attributed to HPV types, Worldwide



# Percentages of HPV DNA-positive Cancers, United States, 1999-2005

	Any HPV	HPV 16/18
<u>Cancer</u>	<u>%</u>	<u>%</u>
Cervix	90	66
Vaginal	75	55
Vulvar	69	49
Anal	91	79
Penile	63	48
Oropharyngeal	72	62

HPV attributable cancers = 26,000 cancers HPV 16/18 attributable cancers = 21,000 cancers

## Annual Cost of HPV-associated Disease, in 2010 U.S. Dollars

Health outcome	Cost (\$ billions)
Cervical cancer screening*	6.6
Cervical cancer	0.4
Other anogenital cancers	0.2
Oropharyngeal cancer	0.3
Anogenital warts	0.3
RRP**	0.2
TOTAL	8.0

<sup>\*</sup>Cervical cancer screening costs: ~ 80% routine screening, ~20% follow-up

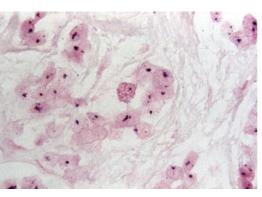
<sup>\*\*</sup>RRP costs: ~ 70% juvenile-onset, ~ 30% adult-onset

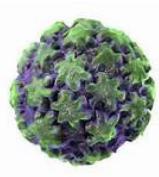
### **Summary**

- □ HPV is a common infection and cause of malignant and non-malignant diseases
  - Causes cancer at a variety of anatomic sites
- Outcomes are burdensome, costly and stigmatizing
- ☐ Approximately 26,000 HPV-attributable cancers
  - 21,000 are vaccine preventable
  - Trends for anal and oropharngeal cancers increasing
  - Racial and ethnic disparities exist
- Cervical cancer screening guidelines
  - Newly harmonized
  - Unchanged for vaccinated individuals, but may change in future

### Overview of HPV Vaccines and Impact Monitoring









#### Eileen F. Dunne, MD, MPH

Medical Officer
Division of STD Prevention
National Center for HIV/AIDS, Viral Hepatitis, STD and TB Prevention



### **HPV Vaccines Licensed by FDA**

	Quadrivalent (Gardasil®)	Bivalent (Cervarix®)
Manufacturer	Merck	GlaxoSmithKline
VLP types	6, 11, 16, 18	16, 18
Licensed in US	Females - 2006 Males - 2009	Females - 2009
Schedule in months from first vaccination	0, 1-2, 6	0, 1-2, 6

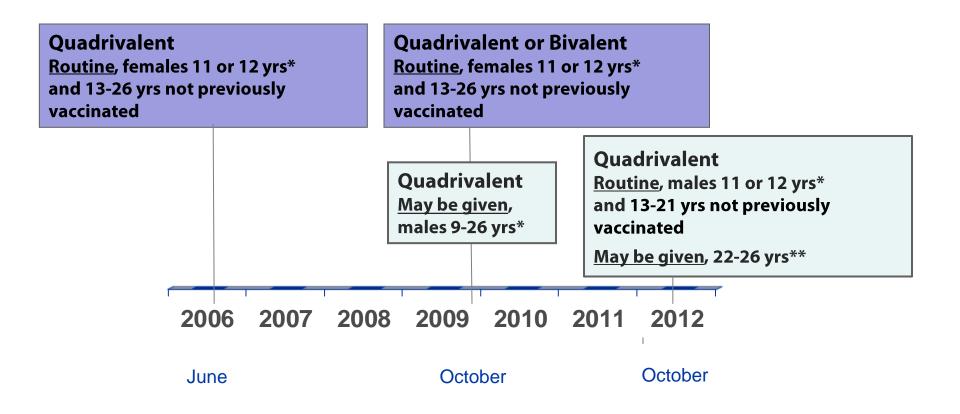
### HPV Vaccine Efficacy in Randomized Controlled Trials

Outcome	Vaccine	Sex	Vaccine Efficacy
Cervical precancer	Bivalent and Quadrivalent	F	>92%
Vaginal/Vulvar precancer	Quadrivalent	F	100%
Anal precancer	Quadrivalent	M	75%
Genital warts	Quadrivalent	F, M	>89%

#### No evidence of efficacy against existing HPV infection or disease

Paavonen J et al. Lancet 2009;374:301-14, Kjaer S et al. Cancer Prev Res 2009;2:868-78, Hildesheim A et al. JAMA 2007;298:743-53, Future I/II Study Group, BMJ 2010;341, The Furture II Study Group Lancet 2007;369:1861-8, Palefsky J et al. NEJM 2011;365:1576-85 Gardasil Package Insert, page 504 Table 12

### **Evolution of Recommendations for HPV Vaccination in the U.S.**



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

<sup>\*</sup> Can be given starting at 9 years of age

<sup>\*\*</sup> For MSM and immunocompromised males, quadrivalent HPV vaccine through 26 years of age

### Current ACIP HPV Vaccine Recommendations Females and Males

- □ Routine vaccination of females aged 11 or 12 years with 3 doses of either bivalent or quadrivalent HPV vaccine
  - ➤ Also for 13 through 26 year olds who have not been vaccinated previously or who have not completed the 3-dose series
- □ Routine vaccination of males aged 11 or 12 years with 3 doses of quadrivalent HPV vaccine
  - Also for 13 through 21 year olds who have not been vaccinated previously or who have not completed the 3-dose series
  - ➤ Gay, bisexual and other men who have sex with men are recommended to receive vaccine through age 26 years

### **Monitoring of HPV Vaccines**

Methods

**Examples** 

NSFG, NHANES

Vaccine Safety	Surveillance and Research	VAERS, VSD, CISA
Vaccine Impact on Infection and Disease Burden	Surveillance and Research	NHANES, Administrative data HPV-IMPACT, Cancer Registries
Vaccine Coverage	National Surveys, Registries	NIS-Teen, Immunization Registries

**National Surveys** 

**Objectives** 

**Behaviors and Attitudes** 

### Post-licensure Vaccine Safety Monitoring: Rationale

- High safety standards expected for vaccines
  - Products given to healthy populations for prevention of disease
- Pre-licensure trials are often too small to detect rare events and special populations may not be adequately represented
- Critical to maintain public confidence in immunization, provide timely information

#### **Post-licensure Vaccine Safety Systems**

#### Vaccine Adverse Event Reporting System (VAERS)

- Collaboration between CDC and FDA
  - National spontaneous reporting system
  - Can detect potential vaccine safety concerns (signals) but not designed to assess causality

#### Vaccine Safety Datalink (VSD)

- Collaboration between CDC and 9 managed care organizations
  - ~9.2 million insured members under active surveillance annually
  - Rates, risks estimates calculated
  - Near real time evaluation through Rapid Cycle Analysis (RCA)

#### Clinical Immunization Safety Assessment (CISA)

- Collaboration between CDC and 7 academic medical centers
  - For clinically complex vaccine adverse events and research on biologic mechanisms

### Summary of VSD Safety Evaluation of HPV Vaccine

#### ☐ Findings from the VSD RCA:

- Among 600,588 doses of quadrivalent vaccine administered to females 9-26 years, no significant increased risk for any of the prespecified adverse events after vaccination:
  - Guillain-Barré syndrome, seizures, syncope, appendicitis, stroke, venous thromboembolism, anaphylaxis and other allergic reactions
- ☐ Total doses of quadrivalent HPV vaccine administered through January 2013 within VSD:
  - > 2.07 million doses
    - ~270K doses of quadrivalent HPV vaccine given to males

### Impact on Biologic Outcomes - What is Vaccine-Preventable?

- Cancers: 70% of cervical and ~90% of non-cervical HPV associated cancers are potentially preventable by either vaccine
  - ~21,000 cancer cases each year
- Cervical Pap test abnormalities: 30-70% are potentially preventable by either vaccine
  - ~1 million cervical Pap test abnormalities each year
- Genital warts: 90% of genital warts preventable by quadrivalent vaccine
  - ~ 325,000 genital warts cases each year

### Monitoring Impact on Biologic Outcomes: Current Activities

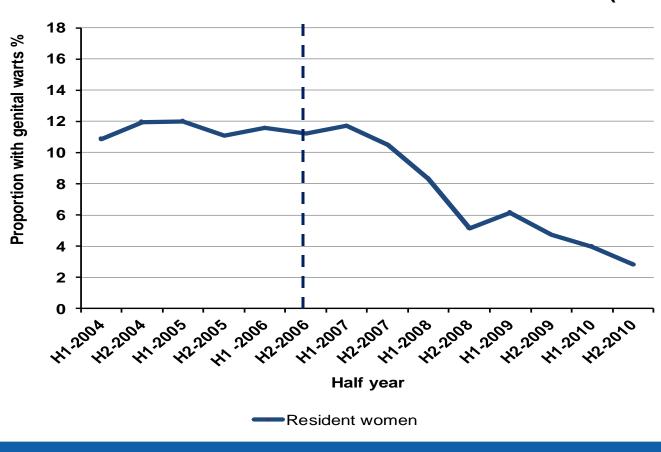
- Surveillance and research to monitor different outcomes
  - Early, mid, late measures
  - National, regional, state
  - General, other populations
- Vaccine effectiveness studies
- Laboratory evaluations
  - > HPV type-specific prevalence for various outcomes
  - U.S. population, precancers, cancers
- Challenges
  - Most outcomes not nationally reportable, many outcomes dependent on cervical cancer screening, varied stakeholder, laboratory testing

## **Monitoring Impact on Biologic Outcomes: Current Activities**

Timeframe	System/study	Outcome
Early	NHANES	HPV type specific prevalence
	Administrative data	Genital warts
Mid	Select cancer registries	Cervical precancers
	HPV-IMPACT	·
Late	Cancer registries	Cervical and other HPV- associated cancers

## Proportion of Women Aged <26 Years with Genital Warts, 2004-2010, Australia

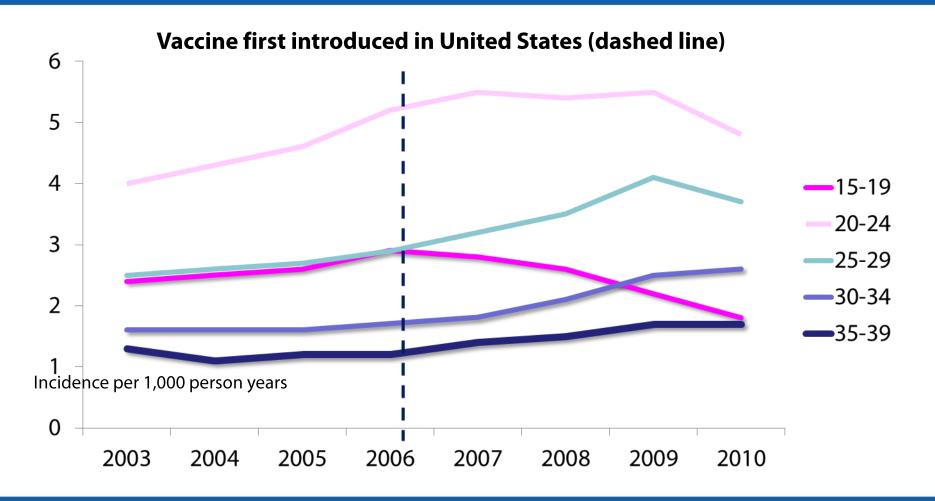
#### Vaccine first introduced in Australia in 2006 (dashed line)



73% decrease in genital warts

Donovan B et al. Lancet Infect Dis 2011;11:39-44

### Genital Warts, Females 2003-2010 by Age Group, U.S. MarketScan® Database



#### **Summary**

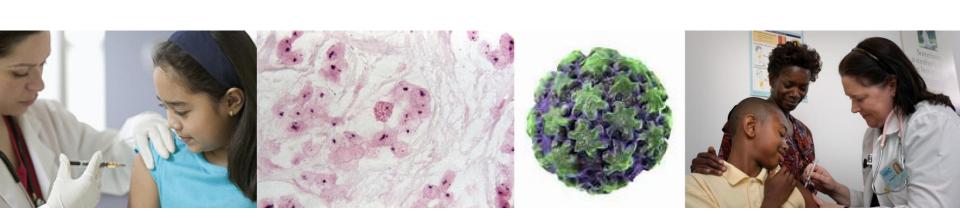
#### HPV Vaccines

- Bivalent and quadrivalent vaccines are safe and effective
- Potential to prevent large burden of cancers and diseases

#### Monitoring

- Ongoing monitoring is important for vaccine program and policy
  - Safety surveillance
  - Biologic outcomes
    - Special evaluations: e.g. effectiveness of less than 3 vaccine doses
- > Early in timeline to measure impact on some biologic outcomes
  - Evidence of impact on genital warts
- Increasing HPV vaccine coverage important to reduce cancers and diseases

### U.S. HPV Vaccination Program: Progress and Challenges



#### **Shannon Stokley, MPH**

Acting Associate Director of Science
Immunization Services Division
National Center for Immunization and Respiratory Diseases



#### **Overview**

- Describe U.S. vaccination program
- Review HPV vaccination coverage levels
- Summarize factors contributing to less than optimal vaccination coverage

### **U.S. HPV Vaccination Program**

- HPV is one of several vaccines recommended for the adolescent age group ("adolescent platform")
  - Tdap, MCV4, annual influenza
- Majority (83%) of vaccines are administered in primary care provider offices and publicly funded clinics (FQHC, RHC)
  - Vaccines often administered during preventive healthcare visits
- National survey found that 98% of pediatricians and 88% of family physicians stocked and administered HPV vaccine
- Vaccine covered by most private health insurance companies and government insurance programs

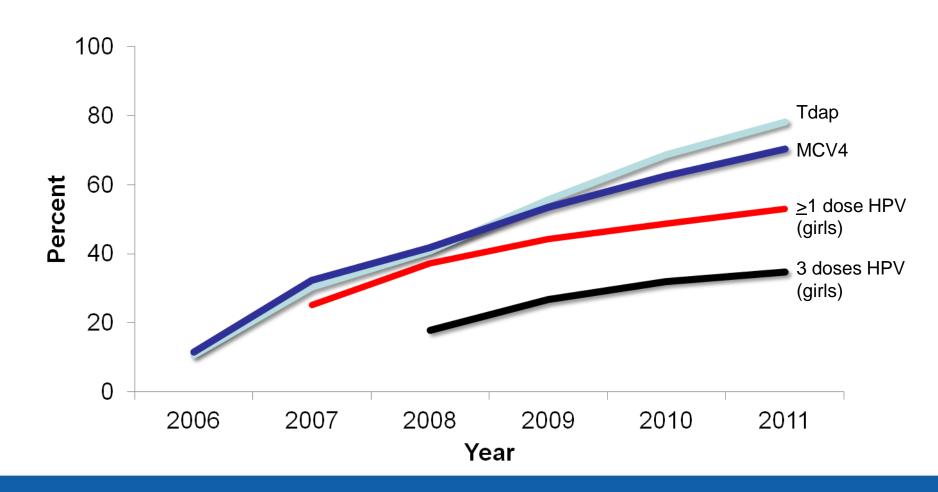
### **Vaccines For Children (VFC) Program**

- □ Federal legislation enacted in 1994 to remove cost as a barrier to vaccination
- ☐ Provides federally purchased vaccines recommended by ACIP at no cost to eligible children 18 years and younger:
  - Medicaid eligible
  - Uninsured
  - > American Indian/Alaska Native descent
  - Underinsured (if vaccinated at an FQHC or RHC)
- □ In 2011, 39.4% of adolescents 13-17 years of age were eligible for VFC vaccine
- ~44,000 immunization providers enrolled in VFC

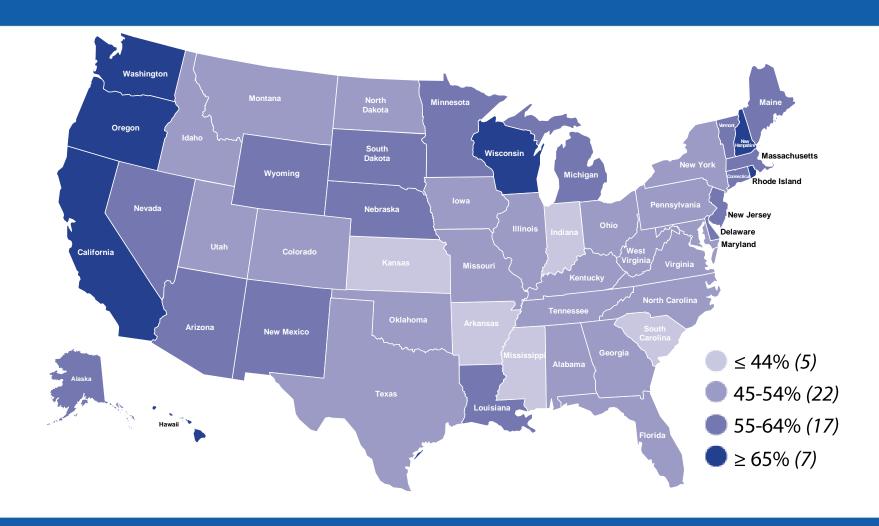
## National Immunization Survey-Teen (NIS-Teen)

- Annual survey
  - Implemented in 2006
  - State level estimates available beginning 2008
- Uses National Immunization Survey (NIS) sample frame methodology
  - Random digit dial telephone survey
  - National sample of parents of adolescents aged 13-17 years
  - Provider record check for verification of immunizations received
- ☐ All analyses limited to adolescents with provider reported immunization histories

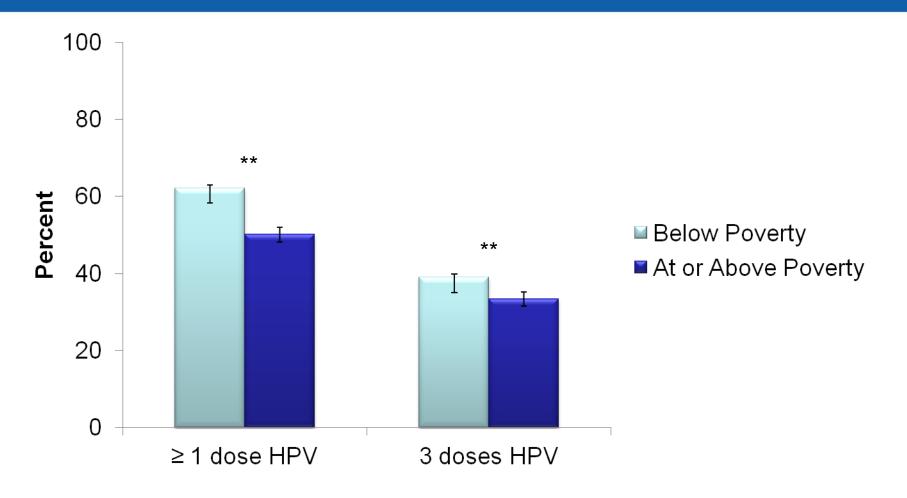
# National Estimated Vaccination Coverage Levels among Adolescents 13-17 Years, NIS-Teen, 2006-2011



### Coverage of 1 of More Doses of HPV among Adolescent Girls 13-17 Years by State, NIS-Teen 2011

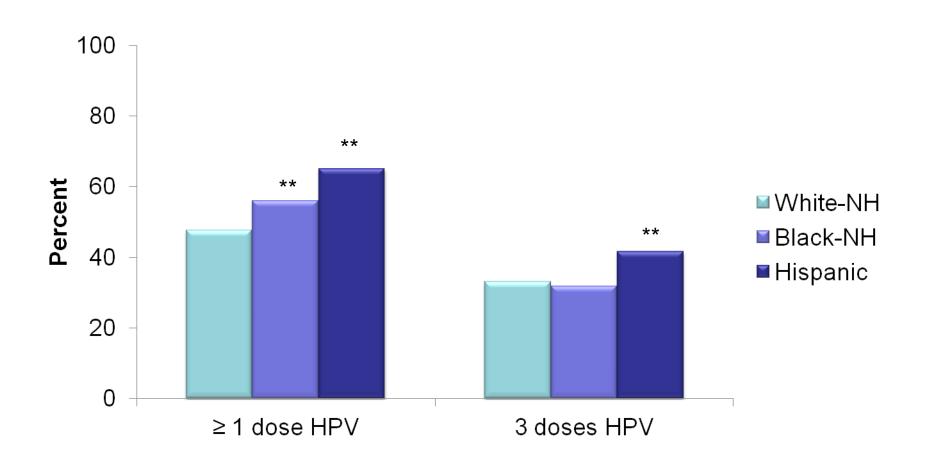


## Vaccination Estimates among Adolescent Girls 13-17 Years by Poverty Status, NIS-Teen 2011



<sup>\*\*</sup> statistically significant (p<0.05)
2011 NIS-Teen available at http://www.cdc.gov/vaccines/stats-surv/nis/nis-2011-released.htm#nisteen

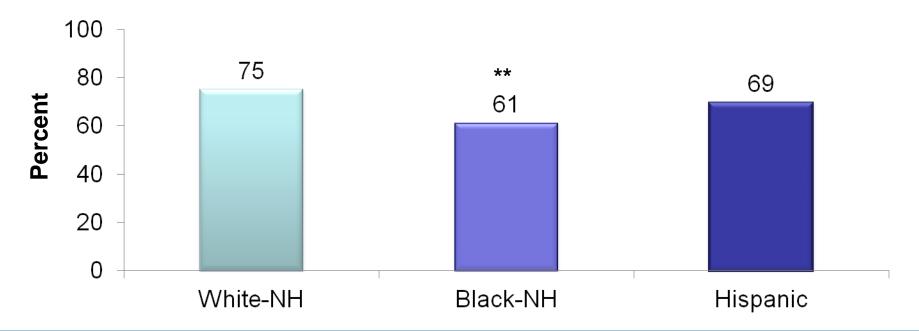
## Vaccination Estimates among Adolescent Girls 13-17 Years by Race/Ethnicity, NIS-Teen 2011



<sup>\*\*</sup> statistically significant (p<0.05)
2011 NIS-Teen available at http://www.cdc.gov/vaccines/stats-surv/nis/nis-2011-released.htm#nisteen

# Completion of the HPV Series among Adolescent Girls 13-17 Years by Race/Ethnicity, NIS-Teen 2011

- Completion: among the girls who started the series, the proportion that received all 3 doses
  - Nationally, 71% of girls that start the HPV series, complete the series.
  - In contrast, population-wide 3-dose coverage was 35% in 2011



<sup>\*\*</sup> Statistically different (P<0.05) from White-NH.

NH: non-Hispanic

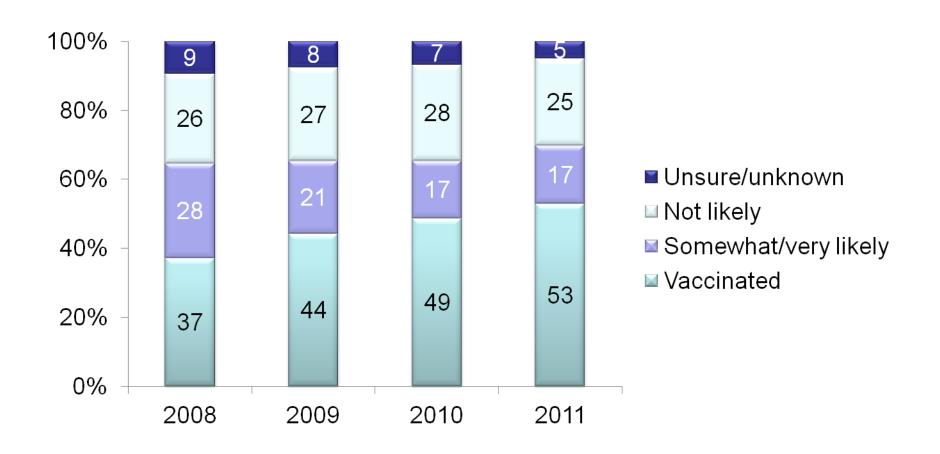
### **HPV Vaccination Uptake among Adolescent Boys**

- Available data represents vaccination activities prior to implementation of routine recommendation approved in October, 2011
- 8.3% of boys 13-17 years of age have initiated the series
- So far vaccine uptake (coverage) follows the same pattern as observed for girls
  - Higher coverage among boys living below the poverty level
  - Higher coverage among Black and Hispanic boys
  - Based on only one year of data

## Challenges in Achieving High Levels of HPV vaccination

- Parental attitudes and vaccine intentions
- Provider attitudes and practices

# HPV Vaccine Intentions (in the Next 12 Months) among Parents of Adolescent Girls 13-17 Years of Age, NIS-Teen

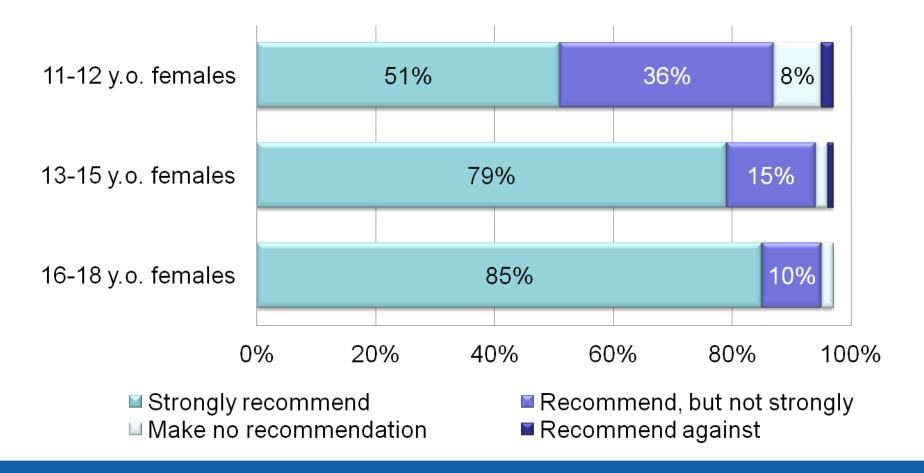


# Most Common Reasons for Not Vaccinating Daughter, among Parents with No Intention to Vaccinate in the Next 12 Months, NIS-Teen 2011

Not needed or necessary	23.2%
Not sexually active	19.5%
Safety concern/side effects	19.3%
Lack of knowledge	15.2%
No recommendation by provider	9.6%

Response categories are not mutually exclusive

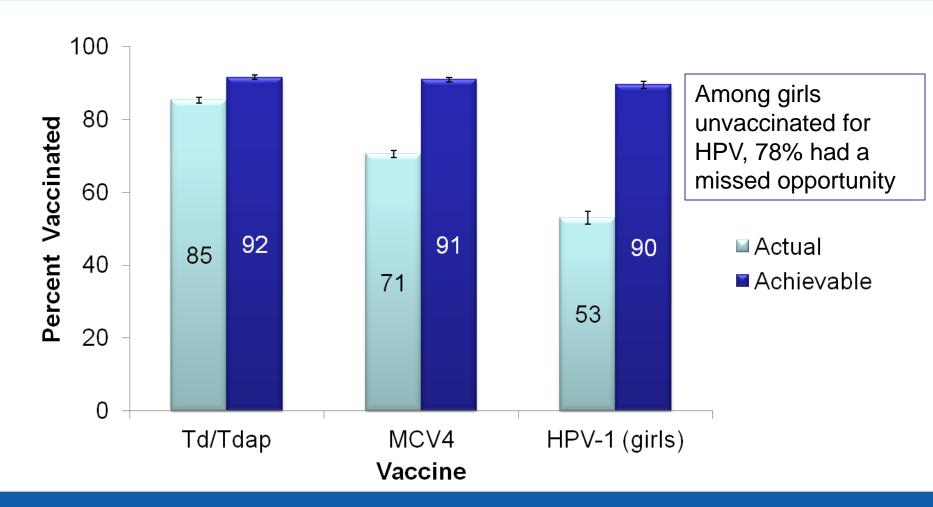
# Strength of HPV Vaccine Recommendation for Female Patients, Pediatricians and Family Physicians (N=609)



### 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

# Actual and Achievable Vaccination Coverage if Missed Opportunities were Eliminated: Adolescents 13-17 Years, NIS-Teen 2011

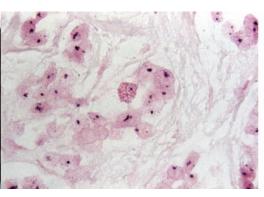


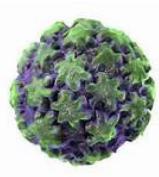
### **Summary**

- HPV vaccination coverage among U.S. adolescent girls is increasing, but slowly
  - Vaccination uptake varies by state
- Efforts are needed to achieve high HPV coverage and subsequent HPV disease prevention:
  - Address provider and parent attitudes towards HPV vaccination
  - Improve communication skills among primary care providers
  - Implement evidence based strategies (e.g. reminder/recall, coverage assessment and feedback) to reduce missed opportunities

## What Is Needed to Increase HPV Vaccine Coverage?









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#### Disclosure

Dr. Middleman's institution receives grants from Novartis and the Society for Adolescent Health and Medicine

### **Increasing HPV Vaccine Coverage**

- Adolescent platform
  - A specific time period during which there is an expectation of vaccine completion
- Public policy strategies
- Provider strategies
  - Practice strategies
  - Provider communication

# ACIP Adolescent Immunization Schedule ("Adolescent Platform")

Vaccines	11-12 yrs	13-15 yrs	16-18 yrs
HPV	3-dose series		
Tdap	1 dose		
MCV4	1 <sup>st</sup> dose		booster
Influenza	,	Annual immunization	1

Range of recommended ages for all children

Range of recommended ages for catch-up immunization

### **Building an Adolescent Immunization Platform**

- Focuses on disease prevention and health promotion among this age group
- Presents opportunities for improved comprehensive care that includes other health issues (e.g., screening and prevention of risk behaviors)
- ☐ Creates parental and provider expectation of adherence to established adolescent vaccine recommendations



### **Increasing HPV Vaccine Coverage**

- Adolescent platform
- Public policy strategies
- Provider strategies
  - Practice strategies
  - Provider communication

### Policy Approaches to Support Adolescent Immunization

- State legislative efforts for school requirements and education
- Utilization of alternative immunization sites
- Health insurance reform

### **Current State Legislation**

#### Middle School requirements

- Vaccination: Td/Tdap: 41 states; MCV4: 13 states;
- > HPV (vaccination: 2 (DC, VA)
- HPV (education): 7 states (WA, LA, NC, MI, IA, TX, IN)

#### General state legislation related to HPV vaccine:

Education of parents/general public (n=14 states)

#### Study of state requirements and coverage

- School requirements: For Tdap and MCV4 significantly higher coverage compared with states no requirements
- Education requirements: for HPV and MCV4, no difference compared with states with no requirements

### Alternative Immunization Sites and Potential Benefits

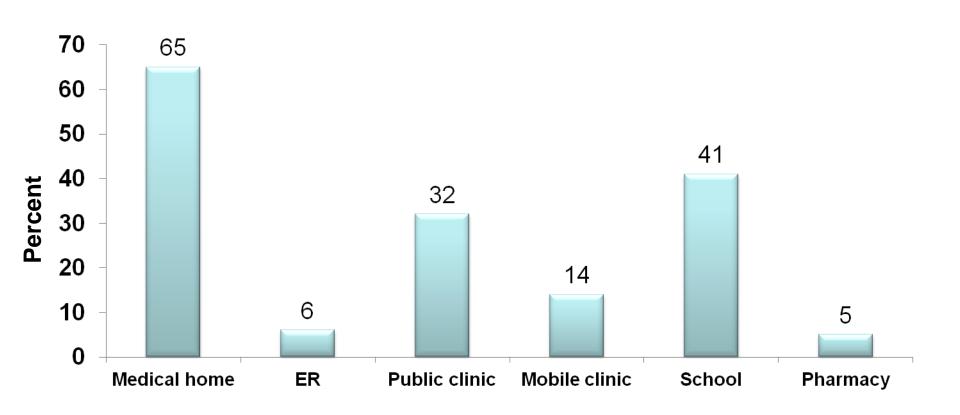
#### Sites

Pharmacies, school-located clinics, city/county clinics, family planning clinics, Ob/Gyn offices and clinics, emergency departments

#### Potential Benefits

- Immunize adolescents who lack a medical home AND provide a list of nearby adolescent medical homes
- Complete multiple-dose regimens
- Provide access (e.g., expanded hours and closer to home)
- Safety of vaccination at alternate sites documented
- Share information with patient's medical home using IIS

## Middle School Parents' Willingness to Use Alternative Sites



#### **School-Located Vaccination**

#### Benefits

- Majority of adolescents attend school
- Potential to vaccinate a large number of adolescents
- Reach many adolescents who may not have regular access to healthcare

#### Challenges

- Adolescent participation may be limited to specific sub-groups
- Cost to provide vaccination in schools can be quite high
- Billing different health plans for immunization services
- Obtaining parental consent

# Preliminary Data From A School-located Immunization Program Targeting VFC-eligible Students in Houston, Fall, 2012

- Approximately 6% of all students returned consent forms
- Among 8 middle schools, 522 eligible students were immunized:

Vaccine	Number Administered
Flu (inactivated and LAIV)	475
Tdap	328
MCV4	327
HPV	410
Other (HepB, varicella, etc.)	82

## Insurance Reforms that Might Impact Vaccine Uptake (Affordable Care Act)

#### First dollar coverage under private insurance

- No out of pocket costs for all ACIP routinely recommended vaccines when given by in-network provider
- In effect September 2010
- Plans have one year following CDC adoption of <u>new</u> ACIP recommendations to implement

### ☐ Increase in Medicaid reimbursement for vaccine administration fee - time limited

- > Time period: 2013-2014
- Before 2013 range: \$2.00 \$17.85
- Proposed fees range: \$19.54 \$27.44

### **Increasing HPV Vaccine Coverage**

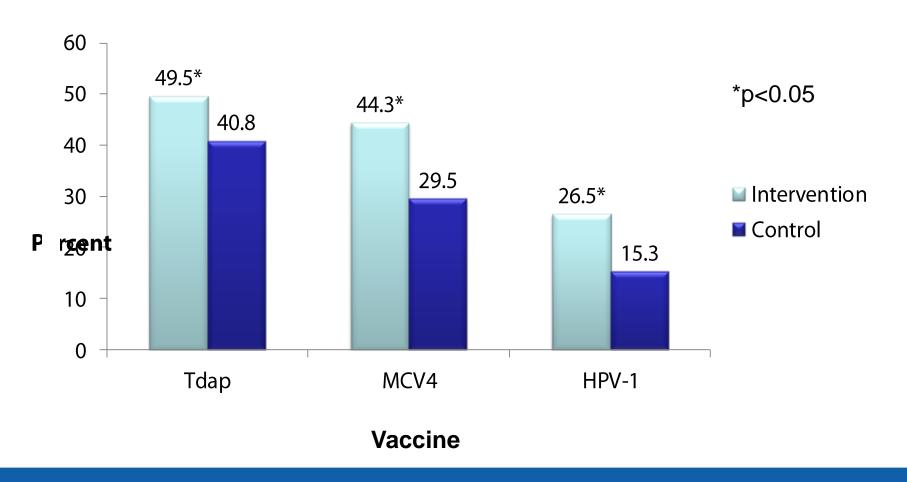
- Adolescent platform
- Public policy strategies
- Provider strategies
  - Practice strategies
  - Provider communication

### Strengthening Immunization in the Medical Home: What Can Providers Do?

- Increase their own knowledge regarding vaccine recommendations and safety of recommended vaccines
- Improve communication with parents
  - Importance of provider recommendation
  - Overall messages
  - Responses to specific concerns
- Initiate practice changes to increase immunization
  - Recall systems
  - Screening tools and standing orders
  - Use of Immunization Information Systems (IIS)
  - Vaccination "quick visits"



## Impact of Reminder and Recall on Vaccination Rates among Adolescents



### **Key Messages for Parents**

- This is a vaccine to prevent CANCER
- The vaccine is SAFE and EFFECTIVE
- The time to give the vaccine is before exposure
- Vaccine is recommended for boys and girls

# Guidance for Providers: Improving the "Discussion"

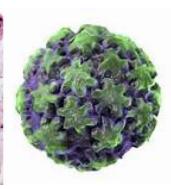
- The discussion regarding mode of HPV transmission should be age appropriate
- Discussion of HPV vaccine might provide an opportunity to discuss sexual health issues, if appropriate
- Vaccination not found to result in increase sexual risk behavior

#### **Take Home Points**

- New immunization recommendations provide enhanced primary prevention opportunities for adolescents
- Public health policies at state and federal levels can be implemented to support adolescent immunization
- Providers can implement communication and quality improvement strategies in the office to improve adolescent immunization rates

### Prevention of HPV-associated Disease Global and Domestic Overview







#### Lauri Markowitz, MD

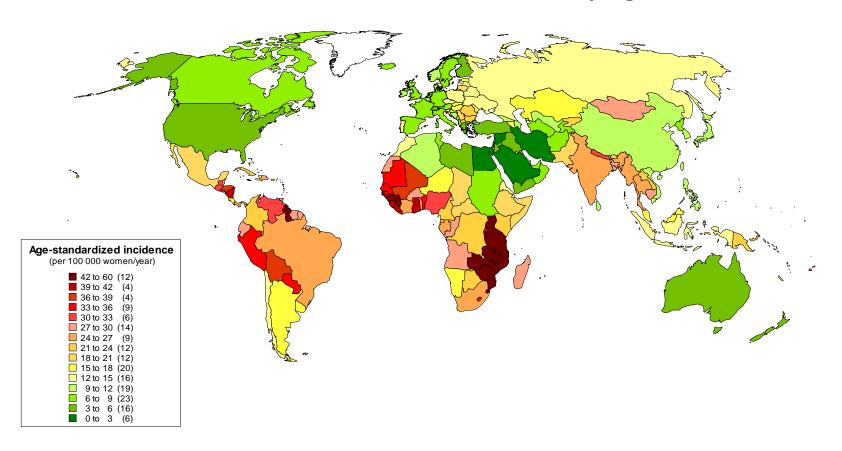
Team Lead
Division of STD Prevention
National Center for HIV/AIDS, Viral Hepatitis, STD and TB Prevention



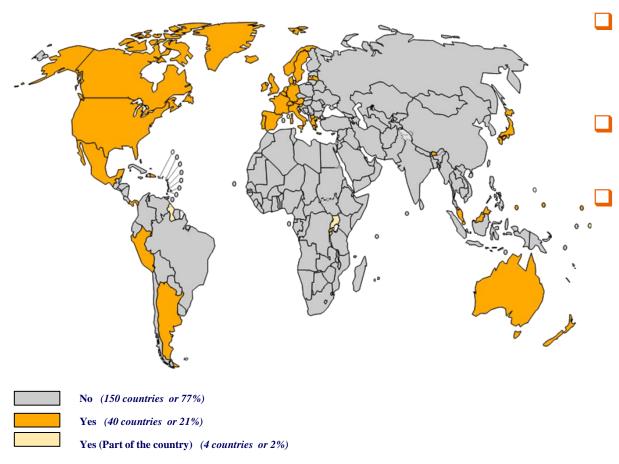
#### **Global Burden of Cervical Cancer**

Incidence of cervical cancer per 100,000 females (all ages), age-standardized 2008

#### 80% of cervical cancer deaths occur in developing countries



## Countries with HPV Vaccine in their National Immunization Schedules, 2011



- HPV vaccination programs have been introduced into more than 40 countries
- Most are developed countries
  - **Challenges:** 
    - Expense of vaccine
    - Competing priorities with other new vaccine introduction
    - Adolescent target age group

#### **International Cervical Cancer Prevention Efforts**

- WHO recommends introduction of HPV vaccination
  - Part of a comprehensive strategy for cervical cancer prevention
- □ Vaccine financing will allow increased HPV vaccine introductions in low resource countries
  - ➤ The Global Alliance on Vaccines and Immunizations (GAVI) will fund HPV vaccine for eligible countries starting in 2013
- Cervical cancer prevention through other public-private partnerships focusing on cervical cancer screening
  - Pink Ribbon Red Ribbon®

(Partners include Susan G. Komen for the Cure, PEPFAR, George W. Bush Foundation, UNAIDS)

### **Summary**

- The substantial burden of HPV-associated disease can be decreased by use of two available safe and effective prophylactic HPV vaccines
- In the United States, vaccine coverage is below target goals
  - Programs are in place to monitor coverage, safety and impact of vaccination
  - Measures can be implemented to improve vaccine uptake
- Progress being made to introduce vaccine in low income countries where most cervical cancer cases and deaths occur