


1:30 – 2:45 pm

An Update on HPV Cancer Prevention

SPEAKERS
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Presenter Disclosure Information

The following relationships exist related to this presentation:

- ▶ Kenneth A. Alexander, MD, PhD: Medical Advisory Board for Merck & Co., Inc. Speakers Bureau for Merck & Co., Inc.
- ▶ Rachel Caskey, MD, MPP: No financial relationships to disclose.

Off-Label/Investigational Discussion

- ▶ In accordance with pmiCME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.

Learning Objectives

At the completion of this activity, participants will be better able to :

1. Summarize the epidemiology and burden of disease associated with the human papilloma virus (HPV)
2. Identify those HPV types most often associated with particular cancers and genital warts
3. Apply strategies to reduce the prevalence of these diseases

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Drug List

<u>Generic</u>	<u>Trade Name</u>
HPV/qHPV	Cervarix, Gardasil
9vHPV	Gardasil 9
Tdap	Adacel, Boostrix
MCV ₄	Menactra, Menveo
MenACWY	

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Approximately 80% of all people are infected by ≥1 type of HPV at some point in their lifetime

Syrjänen K, Syrjänen S. *Scand J Infect Dis Suppl.* 1990;69: 7-17.
 Dunne EF et al. *JAMA.* 2007;297 (8): 813-819.
 Human Papillomavirus. In: Atkinson W et al, eds. *Epidemiology and Prevention of Vaccine-Preventable Diseases*, 12th Edition. Washington DC: The Public Health Foundation/Centers for Disease Control and Prevention; 2011:139-150. <http://www.cdc.gov/vaccines/pubs/pinkbook/downloads/hpv.pdf>. Accessed March 14, 2013.

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HPV-related Cancers and Diseases

- Worldwide, HPV causes ~5% of all new cancers occurring in males and females annually
- Globally, HPVs are responsible for:
 - Virtually 100% of cervical cancers¹
 - 70% of vaginal cancers²
 - 43% of vulvar cancers²
 - Almost all cases of genital warts and RRP
 - 88% of anal cancers³
 - 50% of penile cancers³
 - At least 26% of oropharyngeal cancers³

HPV=human papillomavirus; RRP=recurrent respiratory papillomatosis.

Forman D et al. *Vaccine.* 2012;30 suppl 5:F12-F23; Lacey CJ et al. *Vaccine.* 2006;24 suppl 3:S3/S341.

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Vaccine Composition

- Pseudovirion-based vaccines
 - Based on L1 (capsid) protein
 - Highly immunogenic
- Bivalent vaccine
 - HPV 16, HPV 18 pseudovirions
 - ASO₄ adjuvant
 - Combination of aluminum hydroxide and monophosphoryl lipid A
- Quadrivalent vaccine
 - HPV 6, HPV 11, HPV 16, HPV18 pseudovirions
 - Amorphous aluminum hydroxyphosphate sulfate adjuvant
- 9-valent vaccine
 - HPV 6, 11, 16, 18, 31, 33, 45, 52, 58 pseudovirions
 - Amorphous aluminum hydroxyphosphate sulfate adjuvant

ASO4=Adjuvant System 04.

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Vaccine Composition

- 9-valent vaccine
 - HPV 6, 11, 16, 18, 31, 33, 45, 52, 58 pseudovirions
 - Amorphous aluminum hydroxyphosphate sulfate adjuvant

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qHPV Vaccine Efficacy (Vaccine serotypes, PPE)

- In females
 - 98% for prevention of genital warts and for prevention of CIN2/3 and AIS
- In males
 - 90% for prevention of external genital lesions
 - 75% for prevention of AIN2/3

AIN=anal intraepithelial neoplasia; AIS=adenocarcinoma in situ; CIN=cervical intraepithelial neoplasia; PPE=per-protocol efficacy; qHPV=quadrivalent human papillomavirus.

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**Good, but how good?
(Well, but how well?)**

***If we, as a society, are going to spend
a lot of money on this,
will we get our money's worth?***

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Thinking about end points and time-to-benefit of HPV vaccination

**If you immunize with an HPV vaccine,
how long must you wait until you see clinical benefit?**

It depends on what disease you are talking about.

- Persistent infection: Weeks to months
- Genital warts: Months to 2–3+ years
- Anogenital dysplasias: 2–5+ years
- Anogenital cancers: 10–30+ years
- Oral cancers: 10–30+ years

Franco EL, et al. *J Infect Dis.* 1999;180:1415-23. Moscicki AB. *J Adolesc Health.* 2005;37:53-9. Molano M, et al. *Am J Epidemiol.* 2003;158:486-494. www.cdc.gov/cancer/hpv/statistics/age.htm

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Genital warts in young Australians 5 years into National Human Papillomavirus Vaccination Program: national surveillance data

- Objective
 - Measure the effect on the prevalence of genital warts of the National Human Papillomavirus Vaccination Program in Australia (started in mid-2007).

Ali H et al. *BMJ.* 2013;346:f2032.

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Genital warts in young Australians 5 years into National Human Papillomavirus Vaccination Program: national surveillance data

- Quadrivalent vaccine was used
- Coverage rates decreased with increasing age
 - The **highest rates** were achieved in 12- to 13-year-olds in the school-based program
 - 83% received at least 1 dose
 - **Intermediate rates** were achieved in 20- to 26-year-olds in the community catch-up program
 - 52% received at least 1 dose
 - **Lowest rates** were among women who were aged older than 26 years
- Few males were vaccinated

Genital warts in young Australians 5 years into National Human Papillomavirus Vaccination Program: national surveillance data

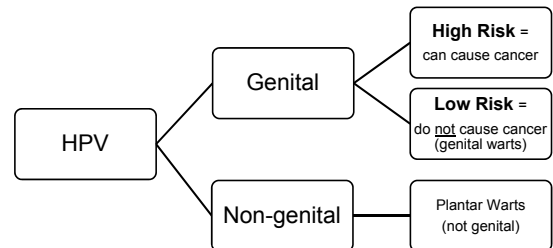
- Conclusions
 - Vaccine efficacy is high
 - The vaccine induces herd immunity
 - The vaccine can reduce disease at a population level

**HPV Infection:
Getting the Facts**

Rachel Caskey, MD, MAPP
Associate Professor of Pediatrics and Internal Medicine
Chief of the Division of General Internal Medicine
University of Illinois at Chicago
Chicago, Illinois

Human Papillomavirus (HPV) in the United States

More than 120 types of HPV



HPV in the United States

HPV is the most common sexually transmitted infection in the United States

- More than 6.2 million new infections every year
- Nearly three-fourths new infections in 15- to 24-year-olds

HPV in the United States

By 50 years old, 80% of women will have acquired a genital HPV infection...

HPV is ubiquitous

HPV in the United States

By 50 years old, 80% of women will have acquired a genital HPV infection...

Most will not develop cancer

Dunne EF et al. JAMA. 2007;297(8):813-819; Centers for Disease Control and Prevention. The Pink Book: Course Textbook. www.cdc.gov/vaccines/pubs/pinkbook/hpv.html. Accessed August 26, 2015.

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Transmission of HPV

Skin-to-Skin Contact!

HPV can spread through anogenital region

- Condoms only partially effective for prevention
- Some adolescents found to test positive for vaginal HPV prior to first vaginal sexual intercourse

Shew ML, Weaver B, et al. Frequent Detection of Vaginal HPV Prior to first Sexual Intercourse during Longitudinal Observation. Journal of Infectious Disease, 2012

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HPV-Related Disease in Adults

- Genital Warts
- Anogenital dysplasias and carcinomas
- Head and neck cancers

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HPV-Related Cancer in 2015

Cancer Type	New Cases	Deaths
Oral, Pharyngeal	45,780	8650
Cervical	12,900	4100
Vaginal and Vulvar	9220	1990
Anal	7270	1010
Penile	1820	310

American Cancer Society. Cancer Facts & Figures 2015. Atlanta: American Cancer Society; 2015.

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Epidemiology of Anal Cancer

- Genital HPV is a risk because HPV can spread throughout the anogenital region
- Anal intercourse significantly increases risk for anal cancer
 - Men who have sex with men at particularly high risk
- Approximately 85% to 90% are associated with HPV
 - 80% HPV16 and 18

Palefsky J, Handley J. What Your Doctor May Not Tell You About HPV and Abnormal Pap Smears. New York, NY: Grand Central Publishing; 2002; Daling JR et al. Cancer. 2004;101(2):270-280; De Vuyst H et al. Int J Cancer. 2009; 124(7):1626-1636; Joseph DA et al. Cancer. 2008;113(10 suppl):2892-2900.

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HPV-Related Cancer in 2015

Incidence of HPV-related oral pharyngeal carcinomas are **increasing**

- Particularly among young males
- 70+% of oropharyngeal carcinomas positive for HPV 16

American Cancer Society. Cancer Facts & Figures 2012. Atlanta: American Cancer Society; 2012; Chaturvedi AK et al. J Clin Oncol. 2008;26(4):612-619; National Cancer Institute. Annual Report to the Nation of the Status of Cancer, 1975-2009. JNCI, 2012; Marur S et al. Lancet Oncol. 2010;11(8):781-789.

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HPV Oropharyngeal Cancers in the United States

- Increase in oropharyngeal cancers in past decades despite decrease in tobacco use
 - Tobacco and alcohol remain risk factors
 - Many HPV+ cancers among never-smokers
- If trend continues, oropharyngeal HPV-related cancers will exceed incidence of cervical cancer in coming years

More MEN with HPV-related cancer than women

American Cancer Society. Cancer Facts & Figures 2012. Atlanta: American Cancer Society; 2012; Chaturvedi AK et al. J Clin Oncol. 2008;26(4):612-619; National Cancer Institute. Annual Report to the Nation of the Status of Cancer, 1975-2009. JNCI, 2012; Marur S et al. Lancet Oncol. 2010;11(8):781-789.

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HPV Oropharyngeal Cancers in the United States

- Transmission is oral sex
 - Though not completely understood
- Why increase in younger individuals?
 - Different sexual norms
 - Earlier oral sex
 - Decrease in other tobacco-related cancers
- Greater prevalence in men?
 - HPV burden in cervix greater than penis

American Cancer Society. Cancer Facts & Figures 2012. Atlanta: American Cancer Society; 2012; Chaturvedi AK et al. J Clin Oncol. 2008;26(4):612-619; National Cancer Institute. Annual Report to the Nation of the Status of Cancer, 1975-2009. JNCI, 2012; Marur S et al. Lancet Oncol. 2010;11(8):781-789.

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Oropharyngeal HPV in the United States

- Oral HPV detected in:
 - 3% to 5% of adolescents
 - 5% to 10% of adults
- HPV vaccines not indicated for prevention of oropharyngeal cancer
 - Not studied in vaccine trials

American Cancer Society. Cancer Facts & Figures 2012. Atlanta: American Cancer Society; 2012; Chaturvedi AK et al. J Clin Oncol. 2008;26(4):612-619; Annual Report to the Nation of the Status of Cancer, 1975-2009. J Natl Cancer Inst. 2013 Jan 7. [Epub ahead of print]; Marur S, et al. Lancet Oncol. 2010;11(8):781-789.

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HPV and SEX

Vaccination against HPV
does NOT affect
sexual behavior

Jena AB et al. JAMA Intern Med. 2015;175(4):617-623; Bednarczyk RA et al. Pediatrics. 2012;130(5):798-805; Mayhew A et al. Pediatrics. 2014;133(3):404-411; Rysavy MB et al. J Pediatr Adolesc Gynecol. 2014;27(2):67-71.

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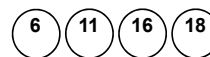
Prevention of HPV-Related
Disease:

Vaccination

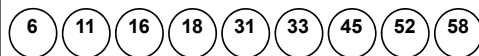
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Is HPV9 Vaccine Better Than HPV4?

HPV4



HPV9



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Is HPV9 Vaccine Better Than HPV4?

<u>Estimated type contribution for certain HPV-related cancer and disease cases</u>	<u>4 HPV types cause:</u> (6, 11, 16, and 18)	<u>9 HPV types cause a total of:</u> (6, 11, 16, 18, 31, 33, 45, 52, and 58)
Cervical cancer cases	70%	90%
Vulvar cancer cases	75%	90%
Vaginal cancer cases	65%	85%
Anal cancer cases	85%	90%–95%
High-grade cervical precancer	50%	80%
Low-grade cervical lesion	25%	50%
Genital warts cases	90%	90%

de Sanjose S et al; Retrospective International Survey and HPV Time Trends Study Group. *Lancet Oncol.* 2010; 11(11):1048-1056; de Sanjose S et al; HPV WAP Study Group. *Eur J Cancer.* 2013;49(16):3450-3461; Alemany L et al; HPV WAP Study Group. *Eur J Cancer.* 2014;50(16):2846-2854; Alemany L et al; HPV WAP Study Group. *Int J Cancer.* 2015;136(1):98-107; Joura EA et al. *Cancer Epidemiol Biomarkers Prev.* 2014; 23(10):1997-2008; Garland SM et al. *J Infect Dis.* 2009;199(6):805-814; Guan P et al. *Int J Cancer.* 2012;131(10):2349-2359.

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Is HPV9 Vaccine Better Than HPV4?

- Clinical study with 14,000 females (16-26yo), received HPV4 or HPV9
 - HPV9 was 97% effective in preventing cervical, vulvar, and vaginal precancerous lesions by 5 additional types
 - HPV9 as effective as HPV4 for the prevention of diseases by 4 shared HPV types by antibody response
- Cost-benefit analysis slightly better than HPV4
 - HPV9 costs approximately \$13 more per dose, but the additional benefit from the 5 types outweighs extra cost

Joura EA et al; Broad Spectrum HPV Vaccine Study. *N Engl J Med.* 2015;372(8):711-723; Centers for Disease Control and Prevention (CDC). *MMWR.* March 27, 2015. Vol 64, #11

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Why Males Only 9 to 15 Years Old?

- Clinical trial data was not complete for males 16-26yo at time of submission to FDA
- Manufacturer has petitioned for an FDA label change for males through age 26 years
- Most insurance companies cover 'per ACIP recommendation' (males and females 9-26 years), but some cover 'per label' (males through 15 years)

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A patient has started the HPV4 series, can I switch?

- All HPV vaccines are interchangeable. You can switch to HPV9 at any point during the vaccine series
- Keep on vaccinating!
 - Use what you have available
 - Do not delay vaccination waiting for HPV9

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Should I give a booster dose of HPV9?

If the 3-dose series of the HPV vaccine has been completed, you do not need to administer a booster dose of HPV9

– Reviewed by ACIP in June 2015

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Strategies to Vaccinate

- Capture missed opportunities
 - Non-primary care visits: acute care visits, urgent care, ED
 - Standing immunization orders
 - Extended immunization hours
 - Flu clinic model
 - HPV: normalize vaccination
- Recall system for subsequent doses

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Strategies to Vaccinate Young Adults

A strong recommendation by YOU

HPV vaccine should be offered to all young adults (through 26 years) *regardless* of:

- Sexual history
- History of abnormal Pap
- History of HPV-positive Pap
- Sexual orientation

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Median Age of Diagnosis

- Breast Cancer 62 years
- Colon Cancer 68 years (men)
72 years (women)
- Prostate Cancer 67 years
- Lung Cancer 72 years

National Cancer Institute. Surveillance, Epidemiology, and End Results Program. <http://seer.cancer.gov>. Accessed August 26, 2015.

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Median Age of Diagnosis

- Oropharynx Cancer 62 years
 - 30% before age 50 years
 - HPV-related typically <50 years
- Anal Cancer 60 years
 - More than 30% before age 55 years
- **Cervical Cancer 47 years**
 - More than 14% before age 35 years

National Cancer Institute. Surveillance, Epidemiology, and End Results Program. <http://seer.cancer.gov/>. Accessed August 26, 2015; Marur S et al. *Lancet Oncol.* 2010;11(8):781-789; Chaturvedi AK et al. *J Clin Oncol.* 2008;26(4):612-619.

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HPV: A Life Course Infection

Prevention during childhood

Disease during adulthood

Infection . . . anytime!

Requires All Our Effort

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New ACIP Recommendations for Use of the 9-Valent HPV vaccine (parallel to recommendations for quadrivalent vaccine)

- The 9-valent HPV vaccine is recommended for routine vaccination of 11- and 12-year-old males and females
- As with the quadrivalent vaccine, immunization may be initiated as young as age 9 years
- The ACIP also recommended catch-up immunization with the 9-valent vaccine for females aged 13-26 years

Petrosky E et al; Centers for Disease Control and Prevention (CDC). *MMWR Morb Mortal Wkly Rep.* 2015;64(11):300-304.

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With older males, keep in mind

- While the quadrivalent vaccine is recommended for catch-up immunization of males through age 21, and is recommended for high-risk males through age 26, the 9-valent vaccine is FDA licensed only in males through age 15
- The ACIP is recommending off-label catch-up immunization of all males aged 16 to 21 years, and off-label immunization of high-risk males aged 22 to 26 years

Petrosky E et al; Centers for Disease Control and Prevention (CDC). *MMWR Morb Mortal Wkly Rep.* 2015;64(11):300-304.

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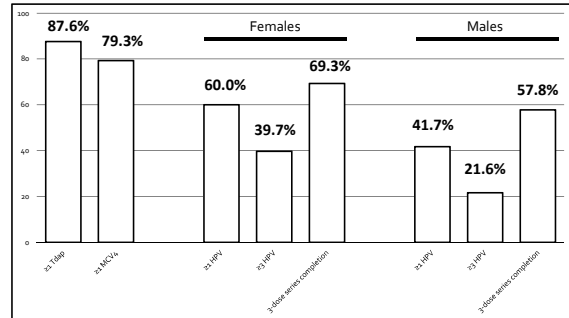
What to do with people who have started, but have not yet completed, the 3-dose series?

- For females, the ACIP does not make a preference among the 2-valent, 4-valent or 9-valent vaccines
- For females, a three-dose series with any of the vaccines is recommended
- For males, a three-dose series with either the 4-valent or 9-valent is recommended

Petrosky E et al; Centers for Disease Control and Prevention (CDC). *MMWR Morb Mortal Wkly Rep.* 2015;64(11):300-304.
Supplemental guidance can be found at <http://www.cdc.gov/vaccines/who/teens/downloads/9vHPV-guidance.pdf>

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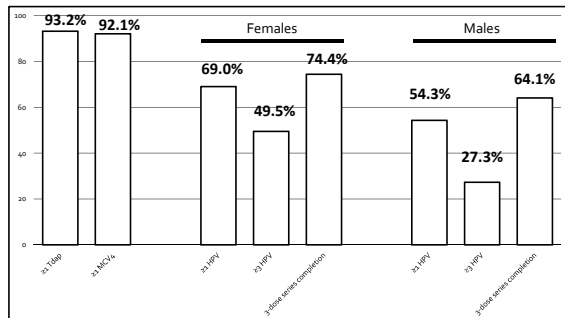
Estimated Vaccination Coverage Among Adolescents Aged 13 to 17 Years, United States, National Immunization Survey–Teen, 2014



Morbidity and Mortality Weekly Report (MMWR) 64(29); 784-792 (2015)

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Estimated Vaccination Coverage Among Adolescents Aged 13 to 17 Years, Massachusetts, National Immunization Survey–Teen, 2014



Morbidity and Mortality Weekly Report (MMWR) 64(29); 784-792 (2015)

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Who are the best physicians to immunize adolescents against HPV?

Pediatric/Family Medicine providers
or
Obstetrician/Gynecologists?

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Why pediatricians and Family Medicine?

Why can't the Obstetrician/Gynecologists do this (especially for HPV)?

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Why Pediatricians and Family Medicine?

- Adolescents need medical homes with providers who understand adolescent issues
- The vaccine works best when given at a younger age
 - Obstetrician/Gynecologists do not care for early teens
- Obstetrician/Gynecologists do not see males
- Obstetrician/Gynecologists are poor immunizers
- Caring for teens is good business
- Pediatric providers are vaccine enthusiasts

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Do We Undervalue HPV Immunization?

- National sample of 776 US physicians (53% pediatricians, 47% family medicine physicians)
- Assessed physicians' perceptions and communication practices related to recommending adolescent vaccines for 11- and 12-year-old patients

Gilkey MB et al. *Prev Med.* 2015;77:181-185.

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Do We Undervalue HPV Immunization?

- For patients aged 11 to 12 years:
 - 95% of physicians reported recommending tetanus, diphtheria, and acellular pertussis (Tdap) as highly important
 - 87% of physicians reported recommending meningococcal conjugate vaccine (MCV4) as highly important
 - 73% of physicians reported recommending HPV vaccine as highly important

Gilkey MB et al. *Prev Med.* 2015;77:181-185.

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Do We Undervalue HPV Immunization?

- 13% of physicians perceived HPV vaccine as being highly important to parents (74% for Tdap, 62% for meningococcal vaccine)
- Among physicians with a preferred order for discussing adolescent vaccines, 70% discussed HPV vaccine last

Gilkey MB et al. *Prev Med.* 2015;77:181-185.

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Each Year in the United States...

- Pertussis kills approximately 20 people per year, mostly young infants
- Meningococcal infections kill approximately 100 people each year
- By vaccinating adolescents with Tdap and MCV4 vaccines, we are working to prevent approximately 120 fatalities per year

Centers for Disease Control and Prevention. 2013 Final Pertussis Surveillance Report. <http://www.cdc.gov/pertussis/downloads/pertuss-surv-report-2013.pdf>. Accessed September 1, 2015.
Centers for Disease Control and Prevention. Active Bacterial Core surveillance (ABCS). <http://www.cdc.gov/abcs/reports-findings/sur-reports.html>. Accessed September 1, 2015.

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And Yet, Each Year in the United States...

- Approximately 4,000 women die of cervical cancer, another 1,900 die of vaginal and vulvar cancer, 1,000 men and women die of anal cancers, and at least 1,700 die of HPV-associated oropharyngeal cancers
- Taken together, timely HPV vaccination could prevent as many as 8,000 to 10,000 HPV-associated cancer deaths

American Cancer Society. *Cancer Facts & Figures 2015*. Atlanta: American Cancer Society; 2015. <http://www.cancer.org/acs/groups/content/@editorial/documents/document/acspc-044552.pdf>. Accessed September 1, 2015.

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Parents make decisions, not on the basis of facts, but on the basis of experience.

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**When we speak doctor-to-doctor,
we use the language of epidemiology.**

We talk about risk...

We use statistics...

Proven facts matter...

**The prospective, double-blinded, placebo-
controlled trial is the standard we demand.**

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**How we talk about HPV immunization
with our patients and in the community
must differ from
how we speak with one another.**

**To best serve our patients,
we must be translators.**

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**When we talk to patients
and in the community,
we must be less scientific
and more emotional.**

We must tell compelling stories.

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**In the United States,
because of our low HPV
immunization rate,
approximately 2500 women
will die each year of preventable
HPV-associated malignancies.**

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**2500 women/year dying of preventable HPV-
associated cancers = One 747 crash every 3 months**

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Two Approaches...

- HPV stands for human papillomavirus
- HPV causes genital warts and cervical cancer
- HPVs are transmitted sexually
- Many adolescents become sexually active by age 13 years
- Do you want this vaccine for your 11-year-old?

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Two Approaches...

- Has anyone that you care about had cancer?
 - What was it like for him or her?
 - What was it like for you?
- We can reduce the chances of your son or daughter having a cancer experience
- Do you want to reduce your child's risk for cancer?

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HPV Tdap meningococcal flu

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When talking with parents about immunization, parents want to know 3 things:

1. Does it work?
2. Is it safe?
3. What is your recommendation?

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Talking With Parents About Immunization

1) Does it work?

Yes!

Vaccine efficacy is high for prevention of cervical disease, genital warts, and anal malignancies. The vaccine may also protect against some head and neck cancers.

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Talking With Parents About Immunization

2) Is it safe?

Yes!

Large clinical trials and extensive post-marketing surveillance have identified sore arms, and the occasional headache and fever, as the only vaccine-associated side effects.

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Talking With Parents About Immunization

3) What is your recommendation?

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Use Every Opportunity to Immunize

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**Nothing you do for children
is ever wasted.**

Garrison Keillor

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