May 1, 2013
8:00 AM – 9:15 AM
Anaheim, California

HPV Immunization
A Model for Cancer Prevention
Session 1: HPV Immunization: A Model for Cancer Prevention

Learning Objectives

1. Explain the epidemiology and burden of disease associated with HPV viruses.
2. Identify those HPV types most often associated with particular cancers and genital warts.
3. Discuss strategies to reduce the prevalence of these diseases.

Faculty

Kenneth A. Alexander, MD, PhD
Professor of Pediatrics
Chief, Section of Pediatric Infectious Diseases
The University of Chicago
Chicago, Illinois

Kenneth A. Alexander, MD, PhD, is professor of pediatrics and chief of the section of pediatric infectious diseases at The University of Chicago, Chicago, Illinois. He attended the University of Washington School of Medicine, Seattle, Washington, where he earned his medical and doctoral degrees. After a pediatric residency at the Children’s Hospital Boston, in Boston, Massachusetts, followed by pediatric infectious diseases fellowship training at Duke University, Durham, North Carolina, Dr. Alexander joined the faculty at Duke. He moved to the University of Chicago in 2005, where he now serves in his current roles in that institute’s pediatric infectious diseases section. Dr. Alexander’s research activities include laboratory studies of human papillomavirus replication, and community-based and school-based promotion of adolescent immunization.

Joel M. Palefsky, MD, CM, FRCP(C)
Professor of Medicine
School of Medicine
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Joel M. Palefsky, MD, CM, FRCP(C), is professor of medicine at the University of California, San Francisco (UCSF) School of Medicine. He completed his undergraduate medical training and training in internal medicine at McGill University, Montreal, Quebec, Canada, and completed a fellowship in infectious diseases at Stanford University in Palo Alto, California. Dr. Palefsky is an internationally recognized expert on the molecular biology, treatment, pathogenesis, and natural history of anogenital human papillomavirus (HPV) infections, particularly in the setting of HIV infection. Director of the Anal Neoplasia Clinic at the UCSF Cancer Center, the world’s first clinic devoted to prevention of anal cancer, he has pioneered diagnostic and treatment methods for anal intraepithelial neoplasia. He is chair of the HPV Working Group of the US National Cancer Institute-supported AIDS Malignancy Consortium and leader of the Pathways to Careers in Clinical and Translational Research program at UCSF. Dr
Palefsky is a member of the board of the American Society for Colposcopy and Cervical Pathology and co-chair of its Special Populations Working Group. He is the author of more than 230 publications.

**Faculty Financial Disclosure Statements**

The presenting faculty reports the following:

Dr Alexander has received advisor, consultant and speaker honoraria from Merck Vaccines.

Dr Palefsky has received grant funding for clinical trials, travel support, and advisor honoraria from Merck & Co, Inc; Dr Palefsky also has received grant funding and speaker honoraria from Hologic; Dr Palefsky also has stock options in Aura Biosciences.

**Education Partner Financial Disclosure Statement**

The content collaborators at Miller Medical Communications, LLC, report the following:

Lyerka D. Miller, PhD, has no financial relationships to disclose.

**Suggested Reading List**


SESSION 1
8:00 AM - 9:15 AM
HPV Immunization: A Model for Cancer Prevention

SPEAKERS
Kenneth A. Alexander, MD, PhD
Joel Palefsky, MD

Presenter Disclosure Information
The following relationships exist related to this presentation:
• Dr Alexander is an advisor, consultant, and speaker for Merck & Co., Inc.
• Dr Palefsky has received grant funding for clinical trials, travel support, and advisor honoraria from Merck & Co, Inc; Dr Palefsky also has received grant funding and speaker honoraria from Hologic; Dr Palefsky also has stock options in Aura Biosciences.

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.

Drug List

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
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<tbody>
<tr>
<td>HPV4</td>
<td>Gardasil</td>
</tr>
<tr>
<td>HPV2</td>
<td>Cervarix</td>
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<tr>
<td>MCV4</td>
<td>Menactra, Menomune, Meningovax</td>
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<tr>
<td>Tdap:</td>
<td>Adacel, Boostrix</td>
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<tr>
<td>Td:</td>
<td>Decavac</td>
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<tr>
<td>MMR:</td>
<td>Attenuvax, Meruvax, Mumpsvax</td>
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<td>Hep A:</td>
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<td>Hep B: E</td>
<td>Engerix-B, Recombivax HB</td>
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<td>Varicella:</td>
<td>Varivax</td>
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<tr>
<td>Influenza:</td>
<td>FluMist, Fluzone, Fluarix, Fluvirin, Fluvir, FluLaval, Afluria, Agriflu</td>
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</table>

(not available in US for 2013)

Learning Objectives
• Explain the epidemiology and burden of disease associated with HPV viruses
• Identify those HPV types most often associated with particular cancers and genital warts
• Discuss strategies to reduce the prevalence of these diseases

Demographic Question

How many adolescents/young adults do you recommend or provide HPV immunization for each week?

1. None
2. 1-10
3. 11-20
4. 21-30
5. Over 30

Outcomes Question 1

HPV is associated with which types of cancers?
1. Genital
2. Anal
3. Oropharyngeal
4. All of the above
5. 1 and 2 only
Outcomes Question 2

Which of the following statements about HPV immunization of males and females is TRUE?

1. Not recommended before age 11
2. Not recommended after age 26
3. There is no catch-up recommendation
4. Not recommended if previous exposure to HPV

Outcomes Question 3

HPV immunization of males is indicated to prevent:

1. Genital warts
2. Anal cancer
3. Oropharyngeal cancer
4. All of the above
5. 1 and 2 only

HPV Immunization:
A Model for Cancer Prevention

Kenneth Alexander, MD, PhD
Professor of Pediatrics
Chief
Section of Pediatric Infectious Diseases
The University of Chicago
Chicago, Illinois

Joel Palefsky, MD, FRCP(C)
Professor of Medicine
University of California, San Francisco
San Francisco, California

Why We Want You to Know About HPV Immunization

• You are respected immunization advocates in the community
• You talk to pediatricians and parents
  ▫ You know about the personal and medical costs of HPV-associated diseases
• You may have children or grandchildren
• Many of you immunize adolescents

Plan for the Hour

• Dr Alexander
  ▫ Update on HPV vaccine recommendations and uptake
  ▫ Discuss adolescent immunization
• Dr Palefsky
  ▫ HPV epidemiology
  ▫ Strategies to improve vaccination
• Dr Alexander
  ▫ Communicating with parents and colleagues about HPV immunization

HPV: Where Are We Now? Where Should We Be Going?

Kenneth Alexander, MD, PhD
Professor of Pediatrics
Chief
Section of Pediatric Infectious Diseases
The University of Chicago
Chicago, Illinois
Six Years of HPV Immunization: Where Are We Now?

- First FDA-licensed indications: June 8, 2006
- For females aged 9-26 years, quadrivalent HPV vaccine is indicated for prevention of the following diseases caused by HPV types 6, 11, 16, and 18:
  - Genital warts
  - Cervical cancer
  - Cervical adenocarcinoma in situ
  - Cervical intraepithelial neoplasia grade 2 and grade 3
  - Cervical intraepithelial neoplasia grade 1
  - Vulvar intraepithelial neoplasia grade 2 and grade 3
  - Vaginal intraepithelial neoplasia grade 2 and grade 3

www.fda.gov.

Six Years of HPV Immunization: Where Are We Now?

- A bivalent vaccine was licensed October 26, 2009
- For females aged 10-25 years, the bivalent HPV vaccine is indicated for prevention of the following diseases caused by HPV types 16 and 18:
  - Cervical cancer
  - Cervical adenocarcinoma in situ
  - Cervical intraepithelial neoplasia grade 2 and grade 3
  - Cervical intraepithelial neoplasia grade 1

www.fda.gov.

Six Years of HPV Immunization: Where Are We Now?

- Since that time, 2 additional indications have been approved by the FDA:
  - Vaccination in boys and men aged 9-26 years for the prevention of genital warts caused by HPV types 6 and 11
  - Vaccination in males and females aged 9-26 years for the prevention of anal cancer and associated precancerous lesions due to HPV types 6, 11, 16, and 18

www.fda.gov.

Current ACIP and AAP Recommendations

- Routine immunization of males and females aged 11-12 years
  - Immunization may be initiated as young as age 9 years
  - Catch-up immunization for females aged 13-26 years
  - Catch-up immunization for males aged 13-21 years
  - Immunization of males aged 22-26 years if not previously immunized
  - Not a strong recommendation due to lack of cost-efficacy models
- Previous sexual activity is not a contraindication to HPV immunization

AAP=American Academy of Pediatrics; ACIP=Advisory Committee on Immunization Practices.
www.cdc.gov/vaccines/pubs/acip-list.htm.

The Quadrivalent HPV Vaccine Is Also Recommended for:

- Gay and bisexual men (or any man who has sex with a man)
- Men and women with compromised immune systems (including people living with HIV/AIDS)

Through age 26 (if they did not get fully vaccinated)

Recommended Adult Immunization Schedule—United States – 2013.

HPV Vaccines — May 2013: Where Are We Now?

- HPV vaccines are safe
- Occasionally, patients faint when immunized
  - Not specific to HPV vaccines
  - Some patients complain of fever or headache

HPV Vaccines — May 2013: Where Are We Now?

- HPV immunization of females and younger males is cost-beneficial
- The community is accepting HPV immunization of females
  - What is happening with boys is less clear
  - Most pediatric practices are giving HPV vaccines routinely to girls
  - Some have started giving the vaccine to boys
- Insurance is paying for HPV vaccination of girls
  - Most are also covering boys


More than 140 countries have now licensed HPV vaccines
- The Australians have shown that immunization of females elicits a herd immunity effect
- Many countries are immunizing girls at school, and are achieving immunization rates much higher than those in the United States


Estimated Vaccination Coverage Among Adolescents Aged 13-17 Years, National Immunization Survey-Teen, US, 2011

- Catch-up immunization of females aged 13-26 years has been disappointing
- Acceptance of male immunization remains low


“HPV vaccines are the first true adolescent vaccines”
Why Is Discussing Immunization of Teens Difficult?

- Discussing immunization forces us to confront many of the messy issues that arise during the transition between childhood and adulthood.

Why is it important that we discuss immunization of teens and young adults?

Vaccines for Teens

<table>
<thead>
<tr>
<th>Year</th>
<th>Vaccine(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>Td</td>
</tr>
<tr>
<td></td>
<td>MCV4 (2 doses)</td>
</tr>
<tr>
<td></td>
<td>HPV (3 doses)</td>
</tr>
<tr>
<td>2013</td>
<td>Tdap (1 dose)</td>
</tr>
<tr>
<td></td>
<td>MCV4 (2 doses)</td>
</tr>
<tr>
<td></td>
<td>HPV (3 doses)</td>
</tr>
<tr>
<td></td>
<td>Hepatitis A (2 doses)</td>
</tr>
<tr>
<td></td>
<td>Influenza (1 dose annually)</td>
</tr>
<tr>
<td></td>
<td>Hepatitis B (Catch-up to 3)</td>
</tr>
<tr>
<td></td>
<td>MMR (Catch-up to 2)</td>
</tr>
<tr>
<td></td>
<td>Varicella (Catch-up to 2)</td>
</tr>
</tbody>
</table>

www.cdc.gov

Some Vaccines That We Wish We Had

- HIV
- HSV
- GC
- RSV
- Chlamydia
- Group B Strep
- Group A Strep
- Staph aureus
- Tuberculosis
- HCV
- Malaria
- Prostate cancer
- Breast cancer
- Stupidity

Vaccines We Wish We Had That Would Likely Be Given to Teenagers

- HIV
- HSV
- GC
- RSV
- Chlamydia
- Group B Strep
- Group A Strep
- Staph aureus
- Tuberculosis
- HCV
- Malaria
- Prostate cancer
- Breast cancer
- Stupidity

www.cdc.gov

MMR=measles, mumps, and rubella.

GS=Neisseria gonorrhoeae (gonococcus); HCV=hepatitis C virus; HIV=human immunodeficiency virus; HSV=herpes simplex virus; RSV=respiratory syncytial virus.
But Wait! There’s More!
Order now and we’ll double your protection
(We’re immunizing females and males)

HPV-related Disease:
The Cervix and Beyond
Joel Palefsky, MD, FRCP(C)
Professor of Medicine
University of California, San Francisco
San Francisco, California

Outline

• Cervical cancer
• HPV-related cancers outside the cervix
  • Anal cancer
  • Vulvar and vaginal cancer
  • Penile cancer
  • Oropharyngeal cancer

HPV Infection and Productive Life Cycle


Spectrum of HPV Disease

HPV-associated Cancers
Two Distinct Patterns Of Epidemiology

• Exclusively (or Nearly) HPV-associated
  • Cervical
  • Anal
  • Partially HPV-associated
    • Penile
    • Vulvar
    • Oropharyngeal
Exclusively (or Nearly) HPV-associated: Cervix, Vagina, and Anus

- Mostly squamous cell cancers
- Risk factors include:
  - Sexual risk factors
  - Smoking
  - Immunosuppression

Epidemiology of Cervical HPV Infection and HPV-associated Disease

Cervical Cancer Incidence

- Cervical cancer prior to cervical cytology screening: 40-50/100,000\(^1\)
- Cervical cancer currently: 8/100,000\(^2\)


Partially HPV-associated: Vulva, Penis, Oropharynx

- The HPV-associated cancers
  - Younger
  - Sexual risk factors
  - Immunosuppression
  - Basaloid or warty on pathology (vulva, penis)

- The non-HPV-associated cancers
  - Older
  - Tobacco and alcohol
  - p53 mutations and poorer prognosis
  - Keratinizing on pathology (vulva, penis)
Penile Cancer

- Overall US age-adjusted incidence rate: 0.81 per 100,000 men\(^1\)
- Approximately 40% of cases are HPV-related
- Associated mortality of 41%\(^2\)
- Survival is \(\leq 2\) years without treatment\(^3\)
- Treatment is associated with substantial psychological and sexual dysfunction\(^4\)
- Constitutes up to 10% of all male cancers in some parts of Africa, Asia, and South America\(^5\)

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HPV Prevalence in Males Enrolled in the HPV Infection in Men (HIM) Study (N=1160) By Age

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Oropharyngeal Cancer

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Incidence of Oropharynx and Cervical Cancers

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Incidence of HPV-Positive and HPV-Negative Oropharynx Cancers

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Image used with permission from Alex Ferenczy, MD.

Anal Cancer in the United States


*2013 data are estimated

Incidence of HPV-associated Cancers in HIV-Cancer Registry Match


Recent Reports of Incidence in Anal Cancer Since Introduction of HAART

- 75/100,000 person-years among HIV+ MSM since 1999
- 78/100,000 person-years among HIV+ MSM since 2000
- 137/100,000 person-years among HIV+ MSM since 1996


Incidence/100,000 (95% CI)

- HIV-infected
  - MSM 131 (109-157)
  - Others 46 (25-77)
  - Women 30 (17-50)
- HIV-uninfected
  - Men 2 (1-4)
  - Women 0 (0-5)

**Anal HPV Infection by Age Group in Sexually Active HIV-Negative MSM**

![Graph showing prevalence of anal HPV infection by age group.]


**Prevalence of Anal HPV Among MSM Population-based Data**

![Bar graph showing prevalence of anal HPV among MSM.]


**Men Who Have Sex With Women Have a High Prevalence of Anal HPV Infection**

![Graph showing overall anal HPV prevalence in MSW.]


**Anal and Cervical HPV Infection in HIV-Positive Women and HIV-Negative Women at High Risk of HIV Infection**

![Graph showing prevalence of anal and cervical HPV infection.]


**Prevalence of Cervical and Anal HPV Infection in Healthy HIV-Negative Women**

![Bar graph showing prevalence of cervical and anal HPV infection.]

N=1566 healthy women who provided cervical and anal specimens.


**Prevalence of AIN Among MSM Population-based Data**

![Bar graph showing prevalence of AIN among MSM.]

AIN in Women With CIN / VIN / VAIN

- Of 205 patients with CIN / VIN / VAIN
  - 12.2% had AIN
  - 8% with AIN 2 or 3


CIN, cervical intraepithelial neoplasia; VIN, vaginal intraepithelial neoplasia; VAIN, vulvar intraepithelial neoplasia.

Other Stuff —Genital Warts—

Figure 53. Genital Warts—Initial Visits to Physicians’ Offices, United States, 1966-2011

Other Stuff —Recurrent Respiratory Papillomatosis—

- Bimodal distribution
  - Early childhood
    - Mother with condyloma
  - Young adulthood
    - Onset of sexual activity

Summary

- HPV infection and its consequences extend beyond the cervix: anus, vulva, vagina, penis, oropharynx
- Secondary prevention in both men and women may reduce their incidence
  - Anus: Anal cytology screening with treatment of HGAIN in groups at high risk for anal cancer
  - Oropharynx: regular oral examinations

HGAIN, high grade anal intraepithelial neoplasia.

Summary

- Primary prevention in both men and women has the potential to reduce their incidence
  - Anus, Vagina, and Vulva Cancer: HPV vaccination approved to prevent cancer due to HPV 16 and 18
  - Oropharynx Cancer: possible but not yet demonstrated
  - Penile Cancer: possible but not yet demonstrated
  - Genital Warts: HPV vaccination approved to prevent warts due to HPV 6 and 11

Advisory Committee on Immunization Practices (ACIP)

- Recommends routine immunization of females aged 11-12 years
  - Catch-up for females aged 13-26 years
  - As early as age 9 years
- Recommends routine immunization of males (affirmative)
  - Aged 11-12 years for prevention of genital warts and anal cancers and precancers
  - Immunization may be initiated as young as age 9 years
  - Catch-up immunization for males aged 13-21 years
- Recommends (permissive)
  - Immunization of males aged 22-26 years for prevention of genital warts and anal cancers and precancers

Are You Crazy?
My 12-year-old patients aren't sexually active!

Good!
They shouldn’t be!

Why Immunize 11- to 12-year-olds Against HPV?

- HPV vaccines are purely preventive
  • To obtain maximal protection, we should immunize before onset of sexual activity

The “Window Period” of Adolescence:
A Gap in US Health Care

Adolescent window period
Ages 12 – 21 years

Peds and FPs
Providers for Adults
0 – 12 years 21 years – death

HPV Vaccine Safety
Adverse Reactions Associated With qHPV Vaccine Use in Females Aged 9-26 Years

- Headache – 28.2% (28.4% placebo)
- Fever – 13% (11.2% placebo)
- Nausea – 6.7% (6.5% placebo)
- Dizziness – 4.0% (3.7% placebo)
- Local injection site reactions – 8.3% (7.5% adjuvant placebo)
- Syncope (sometimes associated with tonic-clonic movements and other seizure-like activity) was not observed in the clinical trials, but was observed in postmarketing surveillance studies. A rate is not reported.

Why Are Teenaged Girls Fainting?

- Why wasn’t fainting seen in the pre-licensure clinical trials?

But What About...

- Guillain-Barré
- Blood clots
- Sudden death

...etc, that patients hear about in the media?

Vaccine Adverse Event Reporting System VAERS

- National passive reporting system
  - Created as part of the National Childhood Vaccine Injury Act (1990)
  - Accepts reports from the public on adverse events associated with vaccines
  - Requires health care providers to report adverse events (possible side effects) that occur following vaccination

Vaccine Adverse Event Reporting System VAERS

- Approximately 30,000 VAERS reports are filed annually
  - 10% to 15% classified as serious (causing disability, hospitalization, life-threatening illness, or death)

VAERS

- VAERS data are unfiltered and lack a denominator

Therefore...

- VAERS cannot be used to test hypotheses
- VAERS can be used to generate hypotheses
Challenges to HPV Immunization

- Our risk-based mindset
  - Makes us think “not my patients”
  - Makes us give the wrong information to parents

Comment From a Colleague:

I'll give the vaccine to my high-risk patients.

Comment From a Colleague:

This is a vaccine for “bad girls” and immoral people.

What Should We Teach Immunizers?

- Risk-based immunization is a failed strategy that leaves the unimmunized at risk of cancer

Many Laypeople Don’t Understand How Vaccines Work

They want to know.

They confuse the vaccine and the disease.

How Do People Make Decisions?

- On the basis of facts that they know, or based on experiences that they have had?
Are We Doing the Right Kinds of Patient Education?

- The rationale for HPV immunization that means something to us may mean little to parents
- Education is an ineffective way to change behavior

- Parents have a great desire to protect their children
- Mothers believe that their children are at risk
- Most parents decide on the basis of experience, not on facts

Two Approaches...

- Our messages to parents may need to be less scientific and more personal and emotional
- To compete with the anti-vaccine people, we need to tell compelling stories

Two Approaches...

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

Talking With Parents About Immunization, Parents Want to Know:

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.
Talking With Parents About Immunization, Parents Want to Know:

2. Is it safe?

Yes
- Large clinical trials have identified sore arms, and the occasional headache and fever as the only vaccine-associated side effects

Talking With Parents About Immunization, Parents Want to Know:

3. What is your recommendation?

Use Every Opportunity to Immunize

Nothing you do for children is ever wasted

Garrison Keillor

Outcomes Question 1

HPV is associated with which types of cancers?

1. Genital
2. Anal
3. Oropharyngeal
4. All of the above
5. 1 and 2 only

Outcomes Question 2

Which of the following statements about HPV immunization of males and females is TRUE?

1. Not recommended before age 11
2. Not recommended after age 26
3. There is no catch-up recommendation
4. Not recommended if previous exposure to HPV
Outcomes Question 3

HPV immunization of males is indicated to prevent:

1. Genital warts
2. Anal cancer
3. Oropharyngeal cancer
4. All of the above
5. 1 and 2 only