Vaccine Updates:
Not a Shot in the Dark

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I have no relationships with any entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients.

I will be discussing off-label indications; all of these are ACIP recommendations.
Objectives

- Discuss and review updates in vaccine recommendations
- Discuss recent changes in vaccine related diseases.
- Identify gaps in clinical practice with regard to vaccine use.
- Specifically for Meningococcal serogroup b, pneumococcus and varicella
What do we want from our vaccines?

- Safe
- Immunogenic
- Efficacious
- Easy (to store, administer, schedule, get paid for)
How are we doing for adults?

Vaccination Rate

Source: CDC - National Health Interview Survey, 2012
HPV vaccine

- New HPV9
  - Adds HPV-31, 33, 45, 52, and 58 to the current qhpv-6,11,16,18
Quiz

Which serotype of HPV is most carcinogenic?

A) 6
B) 11
C) 16
D) 18
E) 31
Genotype attribution to cervical cancer-

Genotype Attribution in Oropharyngeal Cancer

Human papillomavirus prevalence in oropharyngeal cancer cells before vaccine introduction, United States.

Over 90% of anal and cervical cancers and 60% of penile cancers are HPV+.

New Cancer Incidence in 2016

- American Cancer Society Estimate:
  - 16,420 new Oropharyngeal
    - 3,080 deaths
  - 12,990 new Cervical
    - 4,120 deaths
  - 8,080 Anal cancers
    - 1,080 deaths
  - 12,600 Vaginal, Vulvar, and Penile cancers
- Most of these 50,000 cancers are due to HPV.
Current Vaccines for HPV 16 and 18
2 and 4 valent

**Reduce Cervical Infection**
- Reduced incidently detected 6 and 12 month infection by 94% and 91%.

**Reduce Oropharyngeal Infection**
- Estimated Vaccine Efficacy: 93%


How do we make it??

Fig 1. Schematic picture of formation of L1 proteins into HPV VLP.
HPV9
Same protection against 6,11,16, and 18. 96% Effective against the other 5 strains

<table>
<thead>
<tr>
<th>End Point</th>
<th>9vHPV Vaccine (N=7099)</th>
<th>qHPV Vaccine (N=7105)</th>
<th>Risk Reduction (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no./total no.</td>
<td>cases/1000 person-yr</td>
<td>no./total no.</td>
</tr>
<tr>
<td><strong>Modified intention-to-treat population</strong></td>
<td></td>
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</tr>
<tr>
<td>High-grade cervical, vulvar, and vaginal disease†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All participants</td>
<td>340/7027</td>
<td>14.0</td>
<td>344/7027</td>
</tr>
<tr>
<td>HPV-uninfected on day 1</td>
<td>26/3032</td>
<td>2.4</td>
<td>46/3077</td>
</tr>
<tr>
<td>Not related to 9 vaccine HPV types‡</td>
<td>26/3032</td>
<td>2.4</td>
<td>33/3077</td>
</tr>
<tr>
<td>Related to 9 vaccine HPV types‡</td>
<td>0/3032</td>
<td>0.0</td>
<td>13/3077</td>
</tr>
<tr>
<td>HPV-infected on day 1</td>
<td>314/3995</td>
<td>23.1</td>
<td>298/3950</td>
</tr>
<tr>
<td>Not related to 9 vaccine HPV types‡</td>
<td>141/3995</td>
<td>10.0</td>
<td>137/3950</td>
</tr>
<tr>
<td>Related to 9 vaccine HPV types‡</td>
<td>173/3992</td>
<td>12.4</td>
<td>161/3946</td>
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<tr>
<td><strong>Average risk reduction‡</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>High-grade cervical epithelial neoplasia, adenocarcinoma in situ, and cervical cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All participants</td>
<td>325/6882</td>
<td>14.1</td>
<td>326/6871</td>
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<tr>
<td>HPV-uninfected on day 1</td>
<td>26/2976</td>
<td>2.5</td>
<td>44/3009</td>
</tr>
<tr>
<td>Not related to 9 vaccine HPV types‡</td>
<td>26/2976</td>
<td>2.5</td>
<td>31/3009</td>
</tr>
<tr>
<td>Related to 9 vaccine HPV types‡</td>
<td>0/2976</td>
<td>0.0</td>
<td>13/3009</td>
</tr>
<tr>
<td>HPV-infected on day 1</td>
<td>299/3906</td>
<td>23.3</td>
<td>282/3862</td>
</tr>
<tr>
<td>Not related to 9 vaccine HPV types‡</td>
<td>131/3906</td>
<td>10.1</td>
<td>132/3862</td>
</tr>
<tr>
<td>Related to 9 vaccine HPV types‡</td>
<td>168/3906</td>
<td>13.0</td>
<td>150/3862</td>
</tr>
<tr>
<td><strong>Average risk reduction‡</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Per-protocol efficacy population</strong></td>
<td></td>
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<tr>
<td>High-grade cervical, vulvar, and vaginal disease†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Related to HPV-31, 33, 45, 52, or 58</td>
<td>1/6016</td>
<td>0.1</td>
<td>30/6017</td>
</tr>
<tr>
<td>Related to HPV-6, 11, 16, or 18</td>
<td>1/5883</td>
<td>0.1</td>
<td>3/5898</td>
</tr>
<tr>
<td>High-grade cervical epithelial neoplasia, adenocarcinoma in situ, and cervical cancer</td>
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</tbody>
</table>
Where does switching to 9vHPV get us?

Prediction of additional reductions in:

- CIN2/3 precancerous lesions: -19%
- Cervical cancer: -14% *

Vaccination of girls provides most of the benefit.

Overview of cost-effectiveness of 9-valent HPV vaccination  Harrell Chesson, PhD NCHHSTP Centers for Disease Control and Prevention
Advisory Committee on Immunization Practices Meeting  February 26, 2015
CIN: cervical intraepithelial neoplasia.
*US HPV-ADVISE model, after 70 years, in scenario of no cross-protection for 4vHPV.
Slide adapted from Brisson 2014 ACIP.
How effective are we at giving the Vaccine?

NIS-Teen 2013 rates

- National Rates-
  - Girls
    - Receipt of 1 vaccine 57%
    - All 3- 37.6%
      - 70% of those who start series get all 3.
        - Up from 53.8% in 2012
  - Boys
    - 1 Vaccine- 34.6%
      - up from 20.8%
ACIP recs for HPV 9

- 3 dose series- 0,1-2 (FDA 2mo),6mos
- Males- 13-21, MSM or HIV+ to 26
  - (off label-FDA says only 9-15 )
- Females age 11-12 or up to 26 years.
- Catchup- don’t restart, just keep going
- Contraindication- pregnancy
  - HPV4 and 9- yeast allergy
  - HPV2- latex allergy
FAQ-

- What if they have received 3 hpv2 or hpv4 vaccines, should I add the hpv9 to cover those 5 strains?
  - No. The additive benefit isn’t large enough.

- Do we need 2 doses or 3?
  - There is some data for 2 dose qHPV schedule, no data yet for the 9vHPV. (off-label)
Pneumococcal Vaccines

17,000 cases of invasive pneumococcal disease in the US in 2013

Behavioral Risk Factor Surveillance System, (BRFSS) data.
http://www.vdh.state.va.us/epidemiology/immunization/datamanagement/brfss.htm
Pneumococcal Vaccines

PPSV23 Introduced 1983
PCV7 licensed 2000
PCV13 licensed 2010
PCV13 okayed for adults 2012
PCV13 for >65yo 2014
Vaccine effectiveness

- PPSV23 is only moderately effective at protecting against invasive disease (~40% reductions)

- Poor in preventing non-bacteremic pneumococcal pneumonia (NPP)

- NPP is ~10 times more common than bacteremic pneumonia in adults.


Cochrane Review

- “metanalysis does not provide evidence to support the routine use of PPSV to prevent all-cause pneumonia or mortality”
- “strong evidence of PPV efficacy against IPD”

Conjugate vs. Polysaccharide Vaccine

- Induces herd immunity by decreasing nasopharyngeal carriage. (Seen in Hib previously, and monovalent serogroup C vaccine in England.)
- Long term immunity via T-cell activation- may decrease need for booster doses.
Since PCV-7 Vaccine use in children:

- There has been a sustained 45% reduction in invasive disease for all age groups.
- Why could that be???

FIGURE 1. Rate* of vaccine-type (VT) invasive pneumococcal disease (IPD) before and after introduction of pneumococcal conjugate vaccine (PCV7), by age group and year — Active Bacterial Core surveillance, United States, 1998–2003

* Per 100,000 population.
† For each age group, the decrease in VT IPD rate for 2003 compared with the 1998–1999 baseline is statistically significant (p<0.05).
Conjugate Vaccines

- 2011- FDA okays PCV13 for adults >50.
- 2012- ACIP recs PCV13 for adults with certain conditions.
  - Based on:
    - good data on immunocompromised pts from PCV7
    - Immunogenicity data versus PPSV23.
### Whom to vaccinate-ACIP 2012

**Immunocompetent Patients**

PCV 13 is off-label in 19-49 year olds

<table>
<thead>
<tr>
<th>Underlying medical condition</th>
<th>PCV13</th>
<th>PPSV23</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic heart/lung/liver disease</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Diabetics/smokers/alcoholism</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>CSF leak</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

**Immunocompromised Persons**

<table>
<thead>
<tr>
<th>Immunocompromised Persons</th>
<th>PCV13</th>
<th>PPSV23 + 5yr report</th>
</tr>
</thead>
<tbody>
<tr>
<td>renal failure/nephrotic</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Generalized or heme malignancy</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Iatrogenic immunosuppression/xplant</strong></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Congenital or acquired asplenia</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Sickle cell/hemoglobinopathy</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>
Whom to vaccinate-ACIP 2014

- 9/2014-ACIP recommends for all adults >65 years old based on immunogenicity studies.

- “CDC will assess...impact of the recommendation”

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6337a4.htm
How many doses of vaccine is that?

– Put another way, what is the US population >65 years old?

A. 60 million
B. 45 million
C. 20 million
D. 19.7 million
E. 100 million
PCV13 for older adults

One pneumococcal vaccine is covered by Medicare per year.

Patient safety and quality issue - correct vaccine, correct interval.
Intervals from ACIP footnote

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6434a4.htm
Does it work?
PCV13 Efficacy Study

- 84,000 Dutch adults >65yo
  - Randomized- pcv13 vs placebo
- 4 year follow-up
  - 49 cases of vaccine type CAP
    (urinary antigen confirmation)
  - 90 cases in the placebo group
Overall Efficacy for CAP

- **Intention to Treat Efficacy**
  - Vax-type nonbact/noninv CAP - 37.7%
  - Vaccine type invasive disease - 75.8%

- **5.1%(NS) decrease in overall CAP**
  - Non-significant effect
  - We spend more than $13B annually for medicare pts on CAP care (2008 estimate)

- **Limitations**
  - Single country, low IPD rates
FAQs

- What to do in asthma, Crohns, or RA?
  - Can you give before they are immunosuppressed?

- What are the maximum lifetime doses?
  - PCV13 - 1 lifetime dose
  - PPSV23 max of 3 (2, 5yrs apart, then at age 65)

(although with core hospital measures many patients may be getting more than this)
Take Home Points - Pneumococcal vaccines

- We need to vaccinate those over 65 with both PCV13 AND PPSV23.
- Vaccine rate for PPSV23 is still not great.
- Intervals are very confusing, probably matter less than suggested if PCV13 is given first.
- Still need outcomes data for PCV13
Zoster Vaccine

- https://cidutest.files.wordpress.com/2008/03/speedbump-shingles.jpg
At what age would you want to receive the zoster vaccine?

- A) 50 years
- B) 60
- C) 65
- D) 70
- E) right now
- F) never
PHN-Duration of pain

Helgason S et al. BMJ 2000;321:794
Zoster Vaccine-Zostavax

Decreases:

PHN by 66.5 % (P<0.001),
Zoster by 51.3 % (P<0.001).

- Oxman et al, NEJM 2005 352:2271-2284
Problem: Duration of Protection

Decreased Efficacy over time

<table>
<thead>
<tr>
<th>Time Period Since Randomization(^a, y)</th>
<th>No. of PY</th>
<th>Burden of Illness (Zoster Vaccine Group)</th>
<th>Vaccine Efficacy for HZ BOI Point Estimate (95% CI)</th>
<th>Incidence of PHN (Zoster Vaccine Group)</th>
<th>Vaccine Efficacy for Incidence of PHN Point Estimate (95% CI)</th>
<th>Incidence of HZ (Zoster Vaccine Group)</th>
<th>Vaccine Efficacy for Incidence of HZ Point Estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 8(^c)</td>
<td>6564</td>
<td>1.46</td>
<td>46.2 (25.8–61.0)</td>
<td>1.37</td>
<td>27.5 (–37.5 to 66.9)</td>
<td>9.0</td>
<td>31.1 (11.2–47.6)</td>
</tr>
<tr>
<td>Year 9</td>
<td>6280</td>
<td>2.04</td>
<td>27.6 (4.5–45.1)</td>
<td>0.80</td>
<td>60.5 (7.7–87.2)</td>
<td>12.3</td>
<td>6.8 (–16.5 to 26.4)</td>
</tr>
<tr>
<td>Year 10</td>
<td>5005</td>
<td>1.95</td>
<td>33.3 (1.5–54.8)</td>
<td>1.20</td>
<td>44.2 (–21.5 to 79.5)</td>
<td>11.4</td>
<td>14.1 (–11.3 to 34.9)</td>
</tr>
<tr>
<td>Year 11</td>
<td>1470</td>
<td>2.80</td>
<td>7.9 (–48.6 to 42.9)</td>
<td>2.04</td>
<td>11.5 (–100.0 to 81.7)</td>
<td>13.6</td>
<td>–1.7 (–57.1 to 37.9)</td>
</tr>
<tr>
<td>SPS (years 0.0–4.9(^b))</td>
<td>58203</td>
<td>0.73</td>
<td>61.1 (51.1–69.1)</td>
<td>0.46</td>
<td>66.5 (47.5–79.2)</td>
<td>5.4</td>
<td>51.3 (44.2–57.6)</td>
</tr>
<tr>
<td>STPS (years 3.3–7.8(^b))</td>
<td>9967</td>
<td>1.42</td>
<td>50.1 (14.1–71.0)</td>
<td>0.70</td>
<td>60.1 (–8.8 to 86.7)</td>
<td>8.4</td>
<td>39.6 (18.2–55.5)</td>
</tr>
<tr>
<td>LTPS (years 4.7–11.6)</td>
<td>25250</td>
<td>1.74</td>
<td>37.3 (26.7–46.4)</td>
<td>1.27</td>
<td>35.4 (8.8–55.8)</td>
<td>10.3</td>
<td>21.1 (10.9–30.4)</td>
</tr>
</tbody>
</table>

New Adjuvant Subunit Vaccine (HZ/su)

- VZV gpE + AS01$_B$ Adjuvant
- f/u 3.2 years, 2 dose regimen
- Worked better– 97%
  - equal efficacy across ages 50 and up.
- A lot of local reactions and
  - “17.0% of HZ/su recipients...reported symptoms that prevented normal everyday activities”

Lal et al. Efficacy of an Adjuvanted Herpes Zoster Subunit Vaccine in Older Adults
NEJM April 28, 2015 DOI: 10.1056/NEJMoa1501184
PPSV23/Zoster vaccine coadministration

- One study showed GMT’s were different in patients co-administered versus 1 month apart.
- FDA and package insert say separate by one month.
- ACIP and CDC disagree with this recommendation based on flaws with this study.
DRUG INTERACTIONS

In a randomized clinical study, a reduced immune response to ZOSTAVAX as measured by gpELISA was observed in individuals who received concurrent administration of PNEUMOVAX®23 and ZOSTAVAX compared with individuals who received these vaccines 4 weeks apart. Consider administration of the two vaccines separated by at least 4 weeks. (7.1, 14.3)
Concomitant use of PPSV and Zoster vaccine (off label)

- Kaiser, southern Cal.
- Zoster incidence after vaccine compared for those with PPSV within 30 days vs 30d after
- HZ incidence of 4.54 and 4.51 per 1000 person-years, respectively.
- Hazard ratio comparing the HZ rate - 1.19 (95% CI, 0.81–1.74)

Concomitant administration of pneumococcal-23 and zoster vaccines provides adequate herpes zoster coverage
Evaluation of the incidence of herpes zoster after concomitant administration of zoster vaccine and polysaccharide pneumococcal vaccine
Vaccine 29(20) P 3628-32. 2011 Tseng, Hung Fu; Smith, Ning; Sy, Lina S.; Jacobsen, Steven J..
Zoster vaccine indications

- All adults 60yrs and older regardless of prior Zoster.
- Costs ~$300
  - Medicare B doesn’t cover it.
  - Per CMS website, “generally, Part D plans will pay”
Take Home Points - Zoster vaccine

- Duration of protection is a huge issue - the new subunit vaccine may fix.
- **Off-label** - In my opinion (and that of the ACIP) it's ok to give concomitantly with PPSV23.
The END- but which one of the following is NOT a method of developing a currently licensed vaccine?

A) use an entire genomes open reading frames to synthesize proteins in vitro, then inject them in a rodent to see what is immunogenic- find one, then purify it.

B) Make envelope protein form pentamers, then get it to self-assemble to a larger particle.

C) Get a harmless recombinant insect virus to infect a moth ovary, then secrete a target protein.

D) Get a target protein, add HbSag to it, then also add AS01 adjuvant.

E) Take a part of a polysaccharide capsule, and connect it to tetanus toxoid.