Adult Immunization: 2013 Update

Interests, Conflicts, Disclosures

- Interests: many
- Conflicts: few
- Disclosures:
  - Member of DSMB of a trial of pneumococcal conjugate/protein vaccine among Navajo infants (GSK)
  - Will be discussing off-label uses but only as recommended by the Advisory Committee on Immunization Practices

Adult Immunizations: 2013

- New Vaccines and Recommendations:
  - Pertussis
  - Influenza
  - Pneumococcal vaccines
  - Zoster
Pertussis

- Alaska 2012:
  - 356 cases
    - 89 in adults age ≥ 20 years
    - Of 56 with documented immunization history, 35 (63%) not up-to-date

http://www.epi.alaska.gov/id/dod/pertussis/cases.htm (accessed April 1, 2013)

Pertussis in Alaska

- 90 additional cases through March 2
- Age distribution 2012-13 (through March 2)

Tdap (Adacel®, Sanofi Pasteur; Boostrix®, GSK)

- Tetanus toxoid
- Diphtheria toxoid, reduced dose*
- Acellular pertussis, reduced dose*
  - *relative to DTaP
- 2005: initial licensure; no safety data for:
  - Administration <5 years following Td, DTaP, or DTwP
  - Adults ≥ 65 years
  - Pregnant women

2013 ACIP Recommendations

- Adults 19-64 years: 1 dose Tdap* regardless of interval since last Td
  - "while longer intervals between Td and Tdap vaccination could decrease the occurrence of local reactions, the benefits of protection against pertussis outweigh the potential risk for adverse events"
- Adults ≥ 65 years: 1 dose* of Tdap
  - Only Boostrix licensed for all persons ≥ 10 years; ACIP: "either vaccine is immunogenic"
- Wound management in adults: Tdap instead of Td
- Pregnant women: 1 dose with each pregnancy, irrespective of history of prior Tdap immunization
  - Optimal timing: 27-36 weeks gestation

* Routine revaccination on ACIP agenda for October 2013 meeting

Why Is A Resurgence of Pertussis?

- Waning vaccine immunity in teens and adults vaccinated during childhood
- More rapid waning of immunity and protection among children vaccinated with DTaP compared with DTwP
- Low uptake of DTaP:
  - <10% of US adults have received Tdap
  - (60% of Alaska Native adult clinical users received Tdap)
- More diagnostic testing with PCR
- ?Disease caused by other Bordetella sp: B. holmesii

Influenza Vaccines

- Which vaccine should be used?
- Does it work?
- Should everyone receive it?

### Which Vaccine?

**Trivalent inactivated vaccines (TIV) for IM administration:** 15µg each antigen/0.5cc dose

**TIV high-dose (Fluzone High Dose®, Sanofi Pasteur):** 60µg each antigen/0.5cc IM dose
  - Licensed for persons aged ≥65 years

**TIV intradermal (Fluzone Intradermal®, Sanofi Pasteur):** 9µg each antigen/0.1cc ID dose
  - Licensed for persons aged 18-64 years

**Trivalent live-attenuated influenza vaccine (LAIV):** FluMist®, Medimmune
  - Licensed for persons aged 2-49 years

### Table: Influenza vaccine information, by age group — United States, 2013-14 influenza season

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Trade name</th>
<th>Manufacturer</th>
<th>Preparation</th>
<th>Antigen concentration</th>
<th>Age group</th>
<th>No of doses</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIV</td>
<td>FluZone™</td>
<td>Sanofi Pasteur</td>
<td>Inactivated</td>
<td>≥60 µg / 0.5cc dose</td>
<td>≥65 years</td>
<td>≥1 dose</td>
<td>IM</td>
</tr>
<tr>
<td>TIV</td>
<td>Fluzone®</td>
<td>Sanofi Pasteur</td>
<td>Inactivated</td>
<td>60 µg / 0.5cc dose</td>
<td>≥65 years</td>
<td>≥1 dose</td>
<td>IM</td>
</tr>
<tr>
<td>TIV</td>
<td>Fluzone High Dose®</td>
<td>Sanofi Pasteur</td>
<td>Inactivated</td>
<td>60 µg / 0.5cc dose</td>
<td>≥65 years</td>
<td>≥1 dose</td>
<td>IM</td>
</tr>
<tr>
<td>TIV</td>
<td>Fluzone Intradermal®</td>
<td>Sanofi Pasteur</td>
<td>Intradermal</td>
<td>9 µg / 0.1cc dose</td>
<td>≥65 years</td>
<td>≥1 dose</td>
<td>ID</td>
</tr>
<tr>
<td>LAIV</td>
<td>FluMist®</td>
<td>Medimmune</td>
<td>Live</td>
<td>≥9 µg / 0.1cc dose</td>
<td>2-49 years</td>
<td>≥1 dose</td>
<td>NM</td>
</tr>
</tbody>
</table>
Which Vaccine? ACIP Recommendations

• Regular TIV vs. high-dose TIV vs. intradermal TIV:
  – “Within specific age indications, ACIP expresses no preference for any given TIV formulation”
• TIV vs. LAIV:
  – “No preference is indicated for LAIV versus TIV in [persons aged 2 through 49 years]”
  – Two exceptions:
    • “persons who care for severely immunosuppressed persons who require a protective environment should not receive LAIV given the theoretical risk for transmission”
    • One other…

MMWR 2012;61:613-8

LAIV or TIV?

• 1952 adults aged 18 to 49 years (mean 23.3 years)
• Randomized to receive TIV or LAIV in double-blind, placebo-controlled trial (5:1:5:1)
• 2007-08: A/H3N2 predominate season; slight drift from vaccine strain
  – Vaccine efficacy, any influenza by culture or PCR:
    • TIV: 68% (95% CI 46% to 81%)
    • LAIV: 36% (95% CI 0% to 59%)
  – Vaccine efficacy, influenza A:
    • TIV: 72% (95% CI 49% to 84%)
    • LAIV: 29% (95% CI -14% to 55%)


LAIV or TIV?

Comparison Among 41,670 Vaccinated Military Service Members (Millennium Cohort) Based in Contiguous US

LAIV or TIV?
Comparison Among 41,670 Vaccinated Military Service Members (Millennium Cohort) Based in Contiguous US

- Healthy personnel aged 18-49; median 27 years; 73% male
- 5,893 ILI events, 168 pneumonia/influenza events

<table>
<thead>
<tr>
<th>Season</th>
<th>LAIV</th>
<th>TIV</th>
<th>Multivariable Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well-Matched</td>
<td>138.5</td>
<td>127.0</td>
<td>0.97 (0.90-1.06)</td>
</tr>
<tr>
<td>Suboptimal Match</td>
<td>149.6</td>
<td>165.1</td>
<td>1.00 (0.90-1.11)</td>
</tr>
</tbody>
</table>


Influenza Vaccine: Does It Work?

- Influenza Vaccine Effectiveness Network

  - Case–control study during the 2012-13 season comparing vaccination histories between
    - 1,115 subjects with ARI documented to be influenza by rRT-PCR
    - 1,582 influenza test-negative controls

- Sites:
  - Seattle, WA (Group Health)
  - Marshfield, WI (Marshfield Clinic)
  - Ann Arbor and Detroit, MI (Univ of Michigan and Henry Ford Health System
  - Pittsburgh, PA (University of Pittsburgh Medical Center)
  - Temple, TX (Scott and White Healthcare)

MMWR 2013; 62:119-123

Influenza Vaccine Effectiveness Network, 2012-13, 2,697 Patients with ARI

<table>
<thead>
<tr>
<th></th>
<th>Influenza + % Vaccinated</th>
<th>Influenza - % Vaccinated</th>
<th>Vaccine Effectiveness (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>33%</td>
<td>50%</td>
<td>56% (47%-63%)</td>
</tr>
<tr>
<td>6 mon-17 yrs</td>
<td>26%</td>
<td>49%</td>
<td>64% (51%-73%)</td>
</tr>
<tr>
<td>18 yrs-49 yrs</td>
<td>28%</td>
<td>42%</td>
<td>52% (38%-79%)</td>
</tr>
<tr>
<td>50 yrs-64 yrs</td>
<td>36%</td>
<td>58%</td>
<td>63% (43%-76%)</td>
</tr>
<tr>
<td>≥65 yrs</td>
<td>69%</td>
<td>72%</td>
<td>27% (31%-59%)</td>
</tr>
<tr>
<td>Influenza A-H3N2</td>
<td>39%</td>
<td>50%</td>
<td>47% (35%-58%)</td>
</tr>
<tr>
<td>Influenza B</td>
<td>25%</td>
<td>47%</td>
<td>67% (51%-78%)</td>
</tr>
</tbody>
</table>

MMWR 2013; 62:119-123
Influenza Vaccine: Does It Work?

- Risk of medically attended influenza and fetal death among 117,347 pregnant women in Norway during 2009 pandemic
  - 54% vaccinated during 2nd or 3rd trimester
  - Vaccine effectiveness 70% (95% CI 66% to 75%)
  - Hazard ratio of fetal loss:
    - Vaccination: 0.88 (95% CI 0.66 to 1.17)
    - Influenza: 1.91 (95% CI 1.07 to 3.41)

- Benefits of vaccinating pregnant women
  - Less influenza illness and risk of death
  - Less fetal loss due to influenza
  - Some immunity during first 6 months of life


Pregnancy and Influenza

- More than just reduced pulmonary capacity...

- PBMCs from pregnant women show attenuated interferon response following stimulation with H1N1 A/2009
- Response is improved following vaccination


Influenza Vaccine: Should Everyone Get It?

- 1960: first national recommendations published in Public Health Reports; based on epidemiology of 1957 pandemic:
  - Persons with chronic diseases
  - Elderly persons
  - Pregnant women
- Next 50 years: expanding recommendations
- 2010: everyone aged ≥6 months
- 2012: new recommendations for patients with history of egg allergy
ACIP: Algorithm for Influenza Immunization of Patients with Egg Allergy

- Can the person eat lightly cooked (e.g. scrambled egg) without reaction?
  - If “yes”, vaccinate
- After eating eggs or egg-containing foods, does the person only develop hives?
  - If “yes”, administer TIV and observe for at least 30 minutes
  - “Persons with egg allergy should receive TIV rather than LAIV” (This is the other no preference exception)
- After eating eggs, does the person experience other symptoms (hypotension, wheezing, nausea/vomiting, other reaction requiring medical attention?)
  - If “yes”, refer before influenza vaccination

MMWR 2012;61:613-8

Influenza Vaccines: More Choices

- For 2013-14: FluMist Quadrivalent® (MedImmune) licensed in 2012
  - A(H1N1)
  - A(H3N2)
  - B/Victoria lineage
  - B/Yamagata lineage
  - Expected to replace trivalent LAIV
- ?QIV

Pneumococcal Vaccines: A Brief History

- 1940s: two 6-valent polysaccharide vaccine briefly on the market
- 1977: 14-valent polysaccharide vaccine (Pneumovax®, Merck)
  - Recommended for persons aged ≥2 years at increased risk for serious pneumococcal infection
- 1983: 23-valent polysaccharide vaccine (PPV-23) (Pneumovax 23®, Merck)
  - Replaces 14-valent vaccine to improve serotype coverage
- 2000: 7-valent pneumococcal conjugate vaccine (PCV-7) (Prevnar®, Wyeth/Pfizer)
  - Serotypes 4, 6B, 9V, 14, 18C, 19F, 23A
  - Recommended for routine infant immunization
- 2010: 13-valent pneumococcal conjugate vaccine (PCV-13) (Prevnar 13®, Wyeth/Pfizer)
  - PCV-7 serotypes plus 1, 3, 5, 6A, 7F, 19A,
  - replaces PCV-7
PCV-13: A Briefer History but…

- Feb 2010
  - Licensed for prevention of IPD and OM in infants and young children (aged 6 weeks through 71 months)
  - ACIP recommends for all children 6 weeks through 59 months and for those 60 months through 71 months with high-risk conditions
- Dec 2010
  - ACIP: "PCV-13 may be administered to children aged 6-18 years" with high-risk conditions, regardless of previous PCV-7 or PPV-23
- Dec 2011
  - Licensed for prevention of pneumonia among adults aged ≥50 years through accelerated approval pathway based on comparison of PCV-13 and PPV-23 antibody responses
- June 2012
  - ACIP recommends PCV-13 for adults aged ≥65 with high-risk conditions
  - ACIP declines to recommend routine use of PCV-13 in adults

Three reasons...

Invasive Pneumococcal Disease Caused by Vaccine Serotypes in Adults, Active Bacterial Core Surveillance, US, 2008

Invasive Pneumococcal Disease, Adults ≥65 Years, ABCS, US, 1998-2007
Colonization With PCV13 Serotypes, Southwestern Alaska, 2008-11

CAPITA Trial

- Community Acquired Pneumonia Immunization Trial in Adults
- Randomized, placebo-controlled trials among 85,000 previously unvaccinated persons aged ≥65 years in the Netherlands
- Primary Outcome: first episodes of vaccine-type CAP
- Secondary Outcomes:
  - Vaccine type invasive pneumococcal infection
  - Non-bacteremic vaccine-type CAP
- Initial enrollment: September 2008
- Estimated primary completion: August 2013

Burden of Pneumococcal Disease, Adults Aged ≥65 Years, US, 2004

- 1.4 million days in-patient care
- 374,000 out-patient clinic visits
- 194,000 emergency department visits
- 16,000 deaths
- $1.8 billion in direct medical costs
  - Note: "...if work loss and productivity are considered, the cost of pneumococcal disease among younger working adults (18–<50) nearly equaled those ≥65"
Estimated Pneumococcal Pneumonia Hospitalizations by Age and Year, US


PCV-13: Not Just For Kids Anymore?

A Recreational Drug?
“We emptied out the HIV wards when we introduced a new drug, I’m begging to feel [that] again. That’s a head rush.”

Emilio Emini, PhD
Senior Vice President and Chief Scientific Officer for Vaccine Research at Pfizer, Inc.

A "Drug of Interest"?
If PCV-13 prevents non-bacteremic pneumococcal pneumonia “the interest of physicians and providers would shift strongly toward that vaccine”

William Schaffner, MD
Vanderbilt University

PCV-13 Recommendations for Immunocompromised Adults Aged ≥19 Years

• Vaccine-naïve:
  – PCV-13 followed by PPV-23 ≥8 weeks later
  – One-time revaccination with PPV-23 5 years after first PPV-23
• Vaccinated with PPV-23 within previous 5 years
  – PCV-13 ≥1 year after last PPV-23 dose
• Vaccinated with PPV-23 ≥5 years previously
  – PCV-13 followed by PPV-23 ≥8 weeks later

MMWR 2012;61:816-9
### Pneumococcal Vaccine Recommendations for Adults, 2013

<table>
<thead>
<tr>
<th>Underlying Medication Condition</th>
<th>PCV-13</th>
<th>PPV-23</th>
<th>PPV-23 Revax*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic cardiopulmonary diseases, diabetes, alcoholism, chronic liver disease, cigarette smoking</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cochlear implant, CSF leak</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Functional or anatomic asplenia</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Immunocompromising condition: HIV, congenital or acquired immunodeficiency, hematologic or generalized malignancy, solid organ transplant</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Everyone aged ≥65 years, regardless of previous vaccination history</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MMWR 2013;61:816-9

### Herpes Zoster

- Reactivation of latent VZV
- 1 million cases in US annually
- Lifetime risk ~30%, 68% in persons aged ≥50 years
- 10% to 18% of persons with herpes zoster develop post-herpetic neuralgia (PHN)
  - 85% of PHN in persons aged ≥5 years
  - Antivirals, steroids: no reduction in PHN risk or severity
- >$1 billion in direct medical costs annually in US


### Medical Claims for Herpes Zoster (ICD-9 code 053.xx), 1993-2006, US

Rates higher among females in all age groups. Rate not related to regional varicella vaccination rates.

Zoster Vaccine

• Zostavax® (Merck), licensed in 2006
• Live attenuated varicella virus (Oka); 14-fold dose in varicella vaccine (Varivax®, Merck)
  – "most attenuated human vaccine"—Mike Oxman
• Randomized, double-blind, placebo-controlled trial among 38,546 adults aged ≥60 years
  – 67% reduction in post-herpetic neuralgia
  – 51% reduction in zoster
  • 64% in 60-69-year-olds
  • 38% in those aged ≥70 years


Zoster Vaccine Recommendations, 2008

• One dose administered immediately after reconstitution (stored frozen)
• All persons aged ≥60 years and older
• Regardless of history of shingles or chickenpox
• Contraindications:
  – Pregnancy
  – Severe immunocompromise
• Transmission of Oka from zoster vaccinee not documented (rare with varicella vaccinees and only those who develop rash)

MMWR 2008;57(RR-5)

Zoster Vaccine Recommendations: New Data

• 2009: Merck revised package insert:
  – Decreased average titer to zoster vaccine when co-administered with 23-valent pneumococcal polysaccharide vaccine (PPV-23), when compared to vaccines administered 4 weeks apart
  – Cohort study in KPSC: 4.54 cases/1,000 person-years with concurrent administration; 4.51/1,000 when PPV-23 administered 30 days to 1 year before zoster vaccine
• 2011: Zoster vaccine licensed for persons aged 50-59 years based on study in Europe
  – 22,439 subjects
  – Zoster rates: 2.0/1,000 person-years with vaccine, 6.6/1,000 with placebo over mean 1.3 years of follow-up
  – Vaccine efficacy: 70% (95% CI 54% to 81%)

Zoster Vaccine Recommendations, 2011

ACIP: No Change

- Declined recommending routine immunization in this age group; reaffirmed recommendation to vaccinate all persons ≥60 years
  - Limited data on long-term protection
  - Production shortfalls
- Declined recommending against co-administration of PPV-23 and zoster vaccine
  - Biological significance of decreased immune response to zoster unknown
  - Requiring multiple visits could create barrier to immunization (uptake still <20%)

The Most Ineffective Vaccines in the World

Table 1: Estimated Cumulative Number of Cases of Selected Infectious Diseases in the United States in the 20th Century before the Advent of a Vaccine, as Compared with Mortality after Utilization.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Estimated Premature Deaths in 20th Century</th>
<th>Deaths in 2002</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smallpox</td>
<td>4.81 million</td>
<td>0</td>
</tr>
<tr>
<td>Poliomyelitis</td>
<td>3.65 million</td>
<td>0</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>17.60 million</td>
<td>2</td>
</tr>
<tr>
<td>Hemagglutinase</td>
<td>3.09 million</td>
<td>22</td>
</tr>
<tr>
<td>Malaria</td>
<td>5.05 million</td>
<td>36</td>
</tr>
<tr>
<td>Whooping Cough</td>
<td>1.92 million</td>
<td>216</td>
</tr>
<tr>
<td>Pertussis</td>
<td>3.47 million</td>
<td>0</td>
</tr>
<tr>
<td>Rubella</td>
<td>4.77 million</td>
<td>20</td>
</tr>
<tr>
<td>Tetanus</td>
<td>0.13 million</td>
<td>13</td>
</tr>
</tbody>
</table>

*Data are from the Centers for Disease Control and Prevention* and Smith and Murphy.

Alaska Division of Public Health Poster, circa 1962