## PRESENTER DISCLOSURES

<table>
<thead>
<tr>
<th>Category</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consultant/ Speakers bureaus</td>
<td>No Disclosures</td>
</tr>
<tr>
<td>Research funding</td>
<td>Agency for Healthcare Research and Quality</td>
</tr>
<tr>
<td></td>
<td>National Institutes of Health</td>
</tr>
<tr>
<td>Stock ownership/Corporate boards-employment</td>
<td>No Disclosures</td>
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<tr>
<td>Off-label uses</td>
<td>No Disclosures</td>
</tr>
</tbody>
</table>
OVERVIEW

• Identify recent changes to the immunization schedule
  • Meningococcal disease, new vaccines and vaccine policy
  • Measles-mumps-rubella vaccines and disease outbreaks
  • Pertussis-containing vaccines and waning immunity
  • Influenza: what’s new with flu
  • Human papillomavirus, opportunity for cancer prevention and a challenge for vaccine uptake

• Evaluate the association between vaccine hesitancy and disease outbreaks
# 2017 VACCINE SCHEDULE

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Birth</th>
<th>1 mo</th>
<th>2 mos</th>
<th>4 mos</th>
<th>6 mos</th>
<th>9 mos</th>
<th>12 mos</th>
<th>15 mos</th>
<th>18 mos</th>
<th>19-23 mos</th>
<th>2-3 yrs</th>
<th>4-6 yrs</th>
<th>7-10 yrs</th>
<th>11-12 yrs</th>
<th>13-15 yrs</th>
<th>16 yrs</th>
<th>17-18 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B (HepB)</td>
<td></td>
<td>1st</td>
<td>2nd</td>
<td>3rd</td>
<td>4th</td>
<td>5th</td>
<td></td>
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<tr>
<td>Rotavirus (RV) RV1 (2-dose series); RV5 (3-dose series)</td>
<td></td>
<td>1st</td>
<td>2nd</td>
<td>3rd</td>
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</tr>
<tr>
<td>Diphtheria, tetanus, &amp; acellular pertussis (DTap &lt;7 yrs)</td>
<td></td>
<td>1st</td>
<td>2nd</td>
<td>3rd</td>
<td>4th</td>
<td></td>
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</tr>
<tr>
<td>Haemophilus influenza type b (Hib)</td>
<td></td>
<td>1st</td>
<td>2nd</td>
<td>See footnote 4</td>
<td></td>
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<tr>
<td>Pneumococcal conjugate (PCV13)</td>
<td></td>
<td>1st</td>
<td>2nd</td>
<td>3rd</td>
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<tr>
<td>Inactivated poliovirus (IPV, &lt;18 yrs)</td>
<td></td>
<td>1st</td>
<td>2nd</td>
<td>3rd</td>
<td>4th</td>
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<tr>
<td>Influenza (IV)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Annual vaccination (IV)</td>
<td>1 or 2 doses</td>
<td>Annual vaccination (IV)</td>
<td>1 dose only</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Measles, mumps, rubella (MMR)</td>
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<tr>
<td>Varicella (VAR)</td>
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<tr>
<td>Hepatitis A (HepA)</td>
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</tr>
<tr>
<td>Meningococcal (Hib-MenCY ≥6 weeks; MenACWY-D ≥9 mos; MenACWY-CRM ≥2 mos)</td>
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<tr>
<td>Tetanus, diphtheria, &amp; acellular pertussis (Tdap ≥7 yrs)</td>
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<tr>
<td>Human papillomavirus (HPV)</td>
<td></td>
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<td></td>
<td></td>
<td>See footnote 13</td>
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</tr>
<tr>
<td>Meningococcal B (MenB)</td>
<td></td>
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<td></td>
<td>See footnote 11</td>
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<td></td>
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<tr>
<td>Pneumococcal polysaccharide (PPSV23)</td>
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<td></td>
<td></td>
<td>See footnote 5</td>
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</tr>
</tbody>
</table>
ACIP UPDATES: 2017-18 SCHEDULE

• Live-attenuated influenza vaccine removed from influenza row

• 16 years has own column to highlight importance of MCV4 booster dose at age 16

• HPV: Blue bar for 9-10 year olds to indicate that this age group can be vaccinated

• New Figure 3 for vaccines that may be indicated (or contraindicated) for children with a medical condition
ACIP UPDATES: FOOTNOTES

• Birth dose HepB: should be given within 24 hours
• Early administration of 4\textsuperscript{th} DTaP: if $\geq$12 months old and $>4$ months from prior dose, no need to repeat
• MCV4: children with HIV a high risk condition
• MenB: 2 dose schedule for MenB-FHbp (Trumenba®)
• HPV: 2 dose series for teens $<15$ years old
• Clarification of schedule for patients who have received OPV
• Tdap in pregnant teens: give vaccine at 27-36 weeks gestation- earlier is better
MENINGOCOCCAL DISEASE, NEW VACCINES AND POLICY
NEISSERIA MENINGITIDIS

• 5 of 13 known serogroups cause disease (A, B, C, Y, W135)

• Transmission via aerosol droplet or contact with respiratory secretions → nasopharyngeal carriage (humans only reservoir)

• Progression to invasive disease depends upon virulence factors and innate susceptibility → 10-14% case fatality rate

• Can cause rapid-onset severe disease due to:
  • Rapid doubling time
  • Endotoxin-rich outer membrane
BURDEN OF DISEASE

- Rates declining since late 1990’s

Meningococcal Incidence in All Ages by Serogroup and Adolescent MenACWY Vaccine Coverage, 1993-2013

- Serogroup B
- Serogroup C
- Serogroup Y

2013: 564 cases (0.18/100,000)

% Coverage with MenACWY among 13-17 year olds

1Source: ABCs cases from 1993-2013 estimated to the U.S. population with 18% correction for under reporting
2National Immunization Survey – Teen; 2006-2013
3NNDSS 2013 final case count

ACIP October 2014
MENINGOCOCCUS B DISEASE OUTBREAKS

• Majority (98%) of meningococcal cases sporadic → risk of outbreaks especially high among different risk groups
• Outbreaks among college students for Men B

<table>
<thead>
<tr>
<th>Site</th>
<th>Year</th>
<th># Cases</th>
<th># Students</th>
</tr>
</thead>
<tbody>
<tr>
<td>University 1</td>
<td>Feb- Mar 2009</td>
<td>4</td>
<td>10,000</td>
</tr>
<tr>
<td>University 2</td>
<td>Nov 2011</td>
<td>2</td>
<td>5,000</td>
</tr>
<tr>
<td>University 3</td>
<td>Jan 2008- Nov 10</td>
<td>13</td>
<td>24,000</td>
</tr>
<tr>
<td>Princeton*</td>
<td>Mar 2013-Mar 2014</td>
<td>9</td>
<td>5,000</td>
</tr>
<tr>
<td>UCSB*</td>
<td>Nov 2013</td>
<td>4</td>
<td>18,000</td>
</tr>
<tr>
<td>Providence College</td>
<td>February 2015</td>
<td>2</td>
<td>4,000</td>
</tr>
<tr>
<td>Univ of Oregon</td>
<td>Jan – June 2015</td>
<td>7</td>
<td>20,000</td>
</tr>
<tr>
<td>Santa Clara University</td>
<td>Jan – Feb 2016</td>
<td>3</td>
<td>5,000</td>
</tr>
</tbody>
</table>

*1400-fold increased risk; +200-fold increased risk
# ACWY Meningococcal Vaccines (U.S.)

<table>
<thead>
<tr>
<th>Vaccine Product</th>
<th>Licensure and Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polysaccharide</td>
<td>Licensed in 1981&lt;br&gt;1 dose for ages ≥ 2 years</td>
</tr>
<tr>
<td>MPSV4 (Menomune)</td>
<td></td>
</tr>
<tr>
<td>Conjugate</td>
<td>Licensed in 2005&lt;br&gt;1-2 doses for ages 2-55 years&lt;br&gt;1-2 doses for ages 9 – 23 months</td>
</tr>
<tr>
<td>MenACWY-D (Menactra)</td>
<td></td>
</tr>
<tr>
<td>MenACWY-CRM (Menveo)</td>
<td>Licensed in 2010&lt;br&gt;1-2 doses for ages 2-55 years&lt;br&gt;2-4 doses for ages 2-23 months</td>
</tr>
<tr>
<td>HibMenCY-TT (MenHibRix)</td>
<td>Licensed in 2012&lt;br&gt;4 dose series for ages 6 weeks – 18 months</td>
</tr>
</tbody>
</table>
ACWY RECOMMENDATIONS

• Routine administration to 11-12 year olds with booster at age 16
  • Waning immunity
  • Importance of circulating antibody for protection

• Routine administration to persons ≥ 2 months old with certain high risk conditions
  • Persistent complement component deficiency
  • Functional or anatomic asplenia
  • Children with human immunodeficiency virus (HIV) infection
  • Community outbreaks
  • Traveling to endemic area
  • 1st year college students (<21 years) in residential housing
  • Microbiologists who work with meningococcus
<table>
<thead>
<tr>
<th>Age Group</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-18 months</td>
<td>HibMenCY-TT or MenACYW-CRM 2, 4, 6 and 12-15 months of age</td>
</tr>
<tr>
<td>-complement deficiency</td>
<td></td>
</tr>
<tr>
<td>-asplenia</td>
<td></td>
</tr>
<tr>
<td>-community outbreak</td>
<td></td>
</tr>
<tr>
<td>9-23 months</td>
<td>MenACYW-D and MenACYW-CRM 2 doses 12 weeks apart</td>
</tr>
<tr>
<td>-complement deficiency</td>
<td></td>
</tr>
<tr>
<td>-travel to endemic area</td>
<td></td>
</tr>
<tr>
<td>-community outbreak</td>
<td></td>
</tr>
<tr>
<td>2 – 55 years</td>
<td>MenACYW-D or –CRM 2 doses 8-12 weeks apart</td>
</tr>
<tr>
<td>-complement deficiency</td>
<td></td>
</tr>
<tr>
<td>-asplenia</td>
<td></td>
</tr>
<tr>
<td>-HIV if also another indication</td>
<td></td>
</tr>
<tr>
<td>2 – 55 years</td>
<td>MenACYW-D or -CRM 1 dose</td>
</tr>
<tr>
<td>-travel to endemic area</td>
<td></td>
</tr>
<tr>
<td>-college student</td>
<td></td>
</tr>
<tr>
<td>-microbiologist</td>
<td></td>
</tr>
</tbody>
</table>
IMPORTANT CAVEATS

• All high risk individuals should receive a booster doses every 5 years:
  • 2-6 year olds receive first booster 3 years after primary immunization then every 5 years thereafter

• Use of MenACYW-D not recommended for 9-23 month olds with sickle cell disease or asplenia
  • Carrier-induced immunosuppression could interfere with response to PCV-13

• HibMenCY-TT not recommended for infants travelling to meningitis belt or Hajj
  • Does not contain A or W-135
INCIDENCE BY AGE AND SEROGROUP

• Serogroup B now causes significant proportion of cases among infants / young children and adolescents/ young adults
SEROGROUP B: THE PROBLEM

- Serogroup B vaccines difficult to make
- Serogroup B polysaccharide mimics a neural cell adhesion molecule (NCAM)
  - Poorly immunogenic
  - Theoretical concern for autoimmunity.
MENINGOCOCCAL GROUP B VACCINES

• Two MenB vaccines are now licensed in the United States for persons 10–25 years of age
  • Trumenba® (Pfizer) licensed on October 29, 2014
  • Bexsero® (Novartis) licensed on January 23, 2015

• Based on immunity to proteins rather than capsular polysaccharides

• Capable of evoking immune responses predictive of protection as measured by serum bactericidal titers
### SEROGROUP B VACCINES

<table>
<thead>
<tr>
<th><strong>TruMenBa® (rLP2086)</strong></th>
<th><strong>Bexsero® (4cMenB)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Tested against 4 prevalent strains in U.S.</td>
<td>• Tested against 3 prevalent strains in U.S.</td>
</tr>
<tr>
<td>• 2 or 3 dose series: 0, 6 or 0, 2 and 6 months</td>
<td>• 2 dose series: 0 and 6 months</td>
</tr>
<tr>
<td>• 8 Phase II and III studies among ~18,000 people</td>
<td>• 4 Phase II and III studies among 8,000 people</td>
</tr>
<tr>
<td>• Local reactions most commonly reported</td>
<td>• Local reactions most common</td>
</tr>
<tr>
<td>• Fever and fatigue most common systemic reactions; no severe adverse events</td>
<td>• Myalgia, fatigue, headache most common systemic symptoms; no severe adverse events</td>
</tr>
</tbody>
</table>
CURRENT ACIP RECOMMENDATION: CATEGORY B

- MenB vaccine series may be administered to adolescents and young adults aged 16–23 years to provide short-term protection against most strains of serogroup B meningococcal disease. The preferred age for MenB vaccination is 16–18 years.
CURRENT RECOMMENDATIONS: CATEGORY A

• Certain persons aged ≥10 years who are at increased risk for meningococcal disease should receive MenB vaccine (recommendation category A)
  • Persons with persistent complement component deficiencies.
  • Persons with anatomic or functional asplenia.
  • Persons who are taking eluzimibab
  • Microbiologists routinely exposed to isolates of *Neisseria meningitidis*.
  • Persons identified as at increased risk because of a serogroup B meningococcal disease outbreak.

¶
**
WHY A CATEGORY B RECOMMENDATION? WHY 16-18 YEAR OLDS?

<table>
<thead>
<tr>
<th>Age</th>
<th>Cases prevented</th>
<th>Deaths prevented</th>
<th>NNV to prevent case</th>
<th>NNV to prevent death</th>
<th>Cost ($) per QALY</th>
</tr>
</thead>
<tbody>
<tr>
<td>11 years</td>
<td>15</td>
<td>2</td>
<td>203,000</td>
<td>1,512,000</td>
<td>8.7</td>
</tr>
<tr>
<td>16 years</td>
<td>28</td>
<td>5</td>
<td>107,000</td>
<td>788,000</td>
<td>4.1</td>
</tr>
<tr>
<td>18 years</td>
<td>29</td>
<td>5</td>
<td>102,000</td>
<td>638,000</td>
<td>3.7</td>
</tr>
<tr>
<td>College students</td>
<td>9</td>
<td>1</td>
<td>368,000</td>
<td>2,297,000</td>
<td>9.4</td>
</tr>
</tbody>
</table>

- Effectiveness data not available (accelerated approval) \(\Rightarrow\) licensure based on bactericidal activity
- Impact on carriage unknown
- No platform for adolescent vaccine administration at 16-18 years
Anti-vaccine activists spark a state’s worst measles outbreak in decades

Penn State's mumps outbreak grows to 36 probable cases

Updated: MARCH 3, 2017 — 2:56 PM EST
MEASLES: A BRIEF REVIEW

• RNA virus in the Paramyxoviridae family
• Humans only natural host

• Spread primarily via **direct contact with infectious droplets**
  • Measles virus can also survive up to 2 hours in fine particles
  • Transmission with Inhalation of small droplets even without face-to-face contact

• Incubation 7 to 21 days (generally 8-12 days)

• Non-specific prodrome → Koplik spots → red, blotchy rash
• Contagious 4 days before to 4 days after rash
# MEASLES COMPLICATIONS

- Children <5 years, adults >20 years, pregnant women, immunocompromised persons

<table>
<thead>
<tr>
<th>Complication</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>8%</td>
</tr>
<tr>
<td>Otitis Media</td>
<td>7-9%</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1-6%</td>
</tr>
<tr>
<td>Encephalitis</td>
<td>1 per 1,000 cases</td>
</tr>
<tr>
<td>Death</td>
<td>1-3 per 1,000 cases</td>
</tr>
<tr>
<td>Subacute Sclerosing Panencephalitis (SSPE)*</td>
<td>1 per 100,000 cases (7-10 years after measles infection)</td>
</tr>
</tbody>
</table>

*fatal degenerative disease of central nervous system: behavioral and intellectual deterioration, seizures
MEASLES IN 2017

• An estimated **20 million cases of measles** occur each year worldwide.

• Current outbreaks in Belgium, France, Germany, Italy, Romania, Guinea, DRC, Indonesia → Travel Notices issued by CDC

• Measles in the U.S.
  
  • **Elimination of endemic measles** in the U.S. in 2000
    • Median annual number of cases declined to 60
  
  • Since 2010, reported cases increasing
    • 2017: 108 cases in 11 states through June 17th
    • 2015: 188 cases (Disneyland)
    • 2014: 667 cases in 23 outbreaks
WHY IS MEASLES RE-EMERGING: A CONFLUENCE OF FACTORS

• Globalization
  • Measles endemic in many countries → majority of US cases imported

• High transmissibility of measles virus
  • Almost all unvaccinated, susceptible individuals exposed to measles will be infected

• Increasing rates of vaccine refusal
  • Majority of affected individuals in current outbreaks unvaccinated, often due to parental choice
VACCINE REFUSAL AND MEASLES IN THE U.S.

• Review of 18 published measles studies (1416 cases) through November 2015
  • 56.8% no history of measles vaccination
  • 16.3% unknown vaccination status
  • 14.1% vaccinated
  • Of 574 unvaccinated individuals who were age-eligible for vaccine, 70.6% unvaccinated due to NON-MEDICAL exemption
  • Children with vaccine exemptions at significantly higher risk for acquiring measles compared to fully vaccinated children (35x)

MUMPS: A BRIEF REVIEW

- Airborne transmission or direct contact with infected droplets
- Not as contagious as measles (more like influenza)

- Incubation period 12-25 days → viremia
- Asymptomatic or nonspecific respiratory infection (20-40%)
- Acute onset of unilateral or bilateral tender swelling of the parotid or salivary glands (9-94%)

COMPLICATIONS:

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<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Orchitis (3-10%)</td>
<td>Mastitis (10%)</td>
<td>Myocarditis (6%)</td>
</tr>
<tr>
<td>Pancreatitis (~4%)</td>
<td>Unilateral deafness</td>
<td>Meningitis (5%) / Encephalitis (~0.5%)</td>
</tr>
</tbody>
</table>
MUMPS IN 2017

99% decrease in incidence of mumps since vaccine introduction but outbreaks still occur

2015-16: outbreaks on several college campuses
WHY OUTBREAKS?

• MMR vaccine effectiveness for mumps ~88% after 2 doses → outbreaks can still occur in highly vaccinated communities

• Outbreak risk higher in crowded environments or with certain behaviors (kissing, sharing utensils, etc)

• BUT complication rate significantly lower among vaccinated individuals

• Waning immunity?
MMR VACCINE

- Live attenuated vaccine
  - Combination MMR licensed in 1971
  - Single-antigen measles vaccine not available in U.S.

- Highly effective
  - 1 dose is 93% effective for measles and 78% effective for mumps
  - 2 doses is 97% effective for measles and 88% effective for mumps
  - Long term and probable lifelong immunity against measles and rubella
MMR VACCINE SAFETY

Excellent safety profile

<table>
<thead>
<tr>
<th>Condition</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever within 6-12 days</td>
<td>5-15%</td>
</tr>
<tr>
<td>Rash</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Febrile seizures in children 12-23 months old</td>
<td>1/3000 doses</td>
</tr>
<tr>
<td>Transient thrombocytopenia</td>
<td>1/25,000 – 1/2 million doses</td>
</tr>
</tbody>
</table>

Contraindications:

- Pregnancy
- Immunodeficiencies with increased risk for viral infection
- Recent receipt of immunoglobulins or steroids
- History anaphylaxis after receiving measles-containing vaccine
  - Gelatin or neomycin - consult an allergist
WHAT ABOUT AUTISM?
VACCINES AND AUTISM

• 1998 publication in *The Lancet* by Wakefield, et al linking autism and MMR
  • Vaccine causes bowel inflammation letting brain-damaging proteins circulate

• Study retracted and findings refuted by multiple studies that have shown no evidence of this link

• Concern has shifted to thimerosal and mercury
• No link found in multiple studies AND even after thimerosal removed from vaccines, autism rates have increased

HAS EVIDENCE REMOVED CONCERN?
POWER OF ANECDOTE

• “Minnesota measles outbreak exceeds last year’s nationwide numbers.”

Measles, mumps and rubella vaccination rates in Minnesota

A growing portion of children of Somali descent are going without an MMR vaccination in Minnesota. The percent of 2-year-olds who were born in Minnesota and have received MMR vaccinations drops between 2004 and 2014 among those of Somali descent compared with those not of Somali descent.

Source: Minnesota Department of Health

PEDIATRIC INFLUENZA: WHAT’S NEW WITH FLU?
INFLUENZA: DEFINITIONS

• Seasonal influenza viruses- circulate yearly
  • A- H1N1 and H3N2
  • B- Yamagata and Victoria
  • C- causes mild disease, sporadic local outbreaks

• Pandemic influenza viruses- new variant to which population has no or limited immunity → large outbreaks
  • A (H1N1) 2009

• Zoonotic or variant influenza- routinely circulate among animals and can sporadically infect humans
  • Usually direct contact with infected animals, no human-to-human transmission
  • Avian influenza A(H5N1), (H9N2); Swine influenza A(H1N1), (H3N2)
INFLUENZA: NOT JUST FOR ADULTS

• Large burden of disease among children

• Hospitalization rates highest among children <5 years → 151/100,000 <1 year and 38.8 / 100,000 1-4 year olds (1993-2008)

Monto & Sullivan, Epidemiol Infect 1993; Zhou H CID 2012
SERIOUS INFLUENZA: WHO’S AT RISK?

• High risk conditions (ACIP/AAP)
  • Asthma
  • Other chronic lung conditions
  • Cardiac disease
  • Chronic renal dysfunction
  • Metabolic/endocrine conditions
  • Long-term salicylate therapy
  • Neurologic/neuromuscular conditions
  • Pregnancy
  • Obesity
SEVERE INFLUENZA IN PREGNANCY

• Pregnant women develop more severe disease
  • Changes in respiratory mechanics and cell-mediated immunity

• During 2009 pandemic, 56 deaths reported among 280 pregnant women admitted to ICUs

• Adverse outcomes also reported for fetus
  • Preterm labor and spontaneous abortion observed in some studies related to severe maternal illness but not consistent
  • Controversy about congenital anomalies such as neural tube defects associated with fever-
FLU VACCINE CATEGORIES

H1N1 FLU
NASAL FLU MIST
HIGH FLU RISK
OVER AGE 65

REGULAR FLU
HIGH DOSE
NEEDLE INJECTION
PREGNANT
AGE 2-49

LOW DOSE
LOW RISK
UNDER AGE 2
PRIORITY JOBS
HEALTH STAFF

ANY QUESTIONS?
**FLU VACCINES FOR CHILDREN: 2017-18**

<table>
<thead>
<tr>
<th>Vaccine Composition</th>
<th>Vaccines</th>
<th>Composition</th>
<th>Age Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quadrivalent Inactivated (IIV4)</td>
<td>Fluarix</td>
<td>intramuscular injection</td>
<td>≥ 36 mo</td>
</tr>
<tr>
<td></td>
<td>Fluzone, <strong>Flulaval</strong>&lt;sup&gt;*&lt;/sup&gt; Afluria</td>
<td></td>
<td>≥ 6 mo</td>
</tr>
<tr>
<td></td>
<td>Afluria</td>
<td>intramuscular injection</td>
<td>≥ 4 years</td>
</tr>
<tr>
<td></td>
<td>Flucelvax</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quadrivalent cell-culture based (ccIIV4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trivalent Inactivated (IIV3)</td>
<td>Afluria</td>
<td>intramuscular injection</td>
<td>≥ 5 years</td>
</tr>
<tr>
<td></td>
<td>Fluvirin</td>
<td></td>
<td>≥ 4 years</td>
</tr>
<tr>
<td></td>
<td>Influvac</td>
<td></td>
<td>≥ 6 mo</td>
</tr>
</tbody>
</table>

*Flulaval IIV4 given as 0.5ml injection for ALL ages)*

**Flu Virus Components:**
A/Michigan/45/2015 (H1N1)pdm09-like virus
A/Hong Kong/4801/2014 (H3N2)-like virus
B/Brisbane/60/2008-like virus

Quadrivalent vaccine also includes a B/Phuket/3073/2013-like virus
ACIP RECOMMENDATIONS 2017-18

Routine vaccination for all persons >6 months old, especially those with high risk conditions

• Offer vaccine by end of October and as long as influenza is circulating

• Children >6 months – 8 years old need 2 doses if first time

• Pregnant women may receive any licensed, recommended and age-appropriate influenza vaccine

• LAIV should not used due to poor effectiveness in 2013-14 and 2015-16 season

• Anyone with history of an egg allergy of ANY severity can receive influenza vaccine
VACCINE EFFECTIVENESS IN CHILDREN: 2009-16

US Flu VE Network: LAIV and IIV VE age 2-17 yrs
Any Influenza A or B

Adjusted Vaccine Effectiveness (%)

<table>
<thead>
<tr>
<th>Year</th>
<th>Virus Type</th>
<th>Total, Flu +</th>
<th>Vaccinated, Flu +</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010-11</td>
<td>Mixed</td>
<td>71</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>H3N2</td>
<td>67</td>
<td>12</td>
</tr>
<tr>
<td>2011-12</td>
<td>H3N2</td>
<td>55</td>
<td>51</td>
</tr>
<tr>
<td>2012-13</td>
<td>H3N2</td>
<td>46</td>
<td>61</td>
</tr>
<tr>
<td>2013-14</td>
<td>H1N1</td>
<td>45</td>
<td>198</td>
</tr>
<tr>
<td>2014-15</td>
<td>H3N2</td>
<td>60</td>
<td>34</td>
</tr>
<tr>
<td>2015-16</td>
<td>H1N1</td>
<td>63</td>
<td>3</td>
</tr>
</tbody>
</table>

ACIP June 2016
LAIV VACCINE EFFECTIVENESS

• Decreased LAIV efficacy most prominent for the quadrivalent vaccine against influenza A (H1N1)pdm09

• Hypotheses:
  • Unique stalk sequence in H1N1 makes hemagluttanin unstable- more difficult to ensure match
  • Potential interference from viruses in the quadrivalent vaccine (i.e. B vaccine component could affect viral replication of the A(H1N1) component
  • Reduced immunogenicity in previously vaccinated children
WHAT ABOUT EGG ALLERGIC PATIENTS?

• Amount of ovalbumin in influenza vaccines is low (micrograms)

• Recent reviews of studies evaluating risk of severe allergic reactions to IIV and LAIV among egg-allergic patients is extremely low
  • Among 4,172 egg allergic patients, no anaphylaxis after receipt of IIV

Anyone with history of egg allergy can receive influenza vaccines

• If severe egg allergy (angioedema, respiratory distress, etc) should receive vaccine in a medical facility under supervision
RE-EMERGENCE OF PERTUSSIS AND PERTUSSIS-CONTAINING VACCINES
PERTUSSIS INCIDENCE IS ON THE RISE

- Incidence increasing since 1980’s, especially among young infants and adolescents
  - 48,277 reported cases (2012); 32,917 (2014)
EPIDEMIOLOGY

• Highly contagious
  • ~90% susceptible exposed household contacts become infected, 50-80% transmission rate in school settings

• Occurs in ALL age groups but disease most severe in young infants who are too young to be fully vaccinated

• Adolescent and adult contacts with unrecognized disease often the reservoir for infection
  • ~30% of infants with pertussis infected from their mother and >40% were infected from other family members
  • Siblings may be most common source of infection
PREVENTION: PERTUSSIS VACCINES

• Acellular pertussis vaccines introduced in 1997 to replace whole cell vaccine (Tdap in 2005)

• Made from purified pertussis antigens and is therefore less reactogenic (3-5 antigens)
  • Moderate reaction (high fever, febrile seizures, inconsolable crying) in ~1/10,000 children

• Immunogenic and effective
  • Comparable efficacy to whole cell vaccine for prevention of moderate to severe disease in pre-licensure studies
IMMUNITY WANES OVER TIME

• Among 15 high prevalence counties in California, estimated vaccine effectiveness for DTaP:
  • >90% for first 3 years after 5th dose
  • 71% >5 years after 5th dose

• Antibody levels substantially decrease within one year of Tdap receipt

WHY DECLINING EFFECTIVENESS?

• Bacteria changing?

• Different immune response elicited by whole cell vs acellular vaccines
  • TH1 response more effective for protective immunity

• Vaccines may not include most immunogenic antigens
VACCINATION REMAINS MOST EFFECTIVE PREVENTION TOOL

• Ensure sufficient population-level immunity to prevent transmission

• 5 dose primary DTaP series at 2, 4, 6, 12-15 months (1997) and 4-6 years (2000)

Tdap

• Routine administration for 11-12 year olds (2005)

• Routine administration for healthcare workers (2006)

• Catch-up vaccination of undervaccinated 7-10 year olds (2010)
IMMUNIZING OTHERS TO PROTECT INFANTS

Cocooning- immunize close contacts of infants to reduce their risk of exposure

- Tdap for ALL adults >18 years old (2012)

- Pregnant women during late 2\textsuperscript{nd} or 3\textsuperscript{rd} trimester or post-partum of EACH pregnancy
  - Maternal Tdap receipt associated with increased antibody titers against pertussis
  - One dose will not provide sufficient protection for subsequent pregnancies
IS IT SAFE TO GIVE TDAP DURING EACH PREGNANCY?

• Reviewed safety data from receipt of Tdap during pregnancy, receipt of >1 Tdap or tetanus toxoid followed by Tdap in non-pregnant adults and receipt of tetanus toxoid during pregnancy

• No unusual patterns of adverse events
  • Fever ~2.4-6%
  • No severe adverse events attributable to vaccination
  • No increased risk for adverse birth outcomes

• Theoretical risk for severe local reactions among women with closely spaced pregnancies
  • Hypersensitivities related to high levels of pre-existing antibody
HUMAN PAPILLOMAVIRUS VACCINES: CHALLENGES AND OPPORTUNITIES
HUMAN PAPILLOMAVIRUS EPIDEMIOLOGY

• Most prevalent sexually transmitted infection
  • 80% men and women infected in lifetime
  • 14 million new cases / per year in US

• HPV disproportionately affects youth
  • 75% new infections in 15-24 year olds
  • 25% 14-19 year olds infected with at least one HPV type

• HPV acquired shortly after sexual initiation even with history of one partner
  • Adolescents: median time to first HPV 3 months
HPV INFECTION AND ANOGENITAL LESIONS

• 130 known serotypes invade cutaneous and mucosal cells of anogenital region, oropharynx and esophagus

• >90% infections spontaneously resolve

• Persistent infection with oncogenic types can lead to progression to neoplastic lesions

• Genetic and epidemiologic evidence suggests HPV is necessary cause of cervical cancer and strongly associated with other anogenital cancers
## CANCERS CAUSED BY HPV, U.S.

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>Average number of cancers per year probably caused by HPV</th>
<th>Percentage per year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Anus</td>
<td>1,600</td>
<td>3,000</td>
</tr>
<tr>
<td>Cervix</td>
<td>0</td>
<td>10,700</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>9,100</td>
<td>2,000</td>
</tr>
<tr>
<td>Penis</td>
<td>700</td>
<td>0</td>
</tr>
<tr>
<td>Rectum</td>
<td>200</td>
<td>500</td>
</tr>
<tr>
<td>Vagina</td>
<td>0</td>
<td>600</td>
</tr>
<tr>
<td>Vulva</td>
<td>0</td>
<td>2,400</td>
</tr>
<tr>
<td>TOTAL</td>
<td>11,600</td>
<td>19,200</td>
</tr>
</tbody>
</table>

CDC, United States Cancer Statistics (USCS), 2006-2010
GENITAL WARTS

• 1 in 10 people will develop genital warts in their lifetime
  • Over 300,000 new cases a year in the US

• High recurrence rate after treatment

• Transmission when asymptomatic

• Infants born to women with genital warts can develop respiratory papillomatosis
AN EFFECTIVE PREVENTION TOOL: HPV VACCINES

- Recombinant L1 capsid proteins that form “virus-like” particles (VLP)
- Non-infectious and non-oncogenic
- Excellent safety and efficacy profile

<table>
<thead>
<tr>
<th>Name</th>
<th>Quadrivalent/HPV4</th>
<th>Bivalent/HPV2</th>
<th>HPV9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Types</td>
<td>6, 11, 16, 18</td>
<td>16, 18</td>
<td>HPV4 + 31, 33, 45, 52, and 58</td>
</tr>
<tr>
<td>Indications</td>
<td><strong>Females</strong>: Anal, cervical, vaginal and vulvar precancer and cancer; Genital warts</td>
<td><strong>Females</strong>: Cervical precancer and cancer</td>
<td><strong>Females</strong>: Anal, cervical, vaginal and vulvar precancer and cancer; Genital warts</td>
</tr>
<tr>
<td></td>
<td><strong>Males</strong>: Anal precancer / cancer; Genital warts</td>
<td><strong>Males</strong>: Not approved for use in males</td>
<td><strong>Males</strong>: Anal precancer/cancer; Genital warts</td>
</tr>
<tr>
<td>Type</td>
<td>HPV-16,18</td>
<td>HPV-31,33,35,52,58</td>
<td></td>
</tr>
<tr>
<td>-----------------------</td>
<td>-----------</td>
<td>-------------------</td>
<td></td>
</tr>
<tr>
<td>Cervical</td>
<td>66%</td>
<td>15%</td>
<td></td>
</tr>
<tr>
<td>Vaginal</td>
<td>55%</td>
<td>18%</td>
<td></td>
</tr>
<tr>
<td>Vulvar</td>
<td>49%</td>
<td>14%</td>
<td></td>
</tr>
<tr>
<td>Anal (M)</td>
<td>79%</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Anal (F)</td>
<td>80%</td>
<td>11%</td>
<td></td>
</tr>
<tr>
<td>Penile</td>
<td>48%</td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td>Oropharynx (M)</td>
<td>63%</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Oropharynx (F)</td>
<td>51%</td>
<td>9%</td>
<td></td>
</tr>
</tbody>
</table>
Proportion of Australian-born women diagnosed with genital warts at first visit, by age group, 2004-11.
# HPV Prevalence Among Females in U.S.: 2003-06 vs 2009-12

<table>
<thead>
<tr>
<th></th>
<th>Pre-vaccine</th>
<th>Post-vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV4 type prevalence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14-19 year olds</td>
<td>11.5%</td>
<td>4.3%</td>
</tr>
<tr>
<td>20-24 year olds</td>
<td>18.5%</td>
<td>12.1%</td>
</tr>
<tr>
<td>Non-vaccinated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sexually active 14-24 year olds</td>
<td>16.9%</td>
<td>2.1%</td>
</tr>
</tbody>
</table>

- No significant reduction in non-vaccine type prevalence suggesting no cross-protection
POPULATION-LEVEL IMPACT OF HPV VACCINATION

- Review of 20 studies in 9 high income countries

- In countries with >50% coverage, among 13-19 year olds
  - HPV 16/18 prevalence decreased at least 68%
  - Anogenital warts decreased by ~61%

- Evidence of herd effects

- Some evidence of cross protection against other types

Drolet et al. Lancet Infect Dis 2015
VACCINE SAFETY

• 3 large post-licensure observational studies + vaccine safety monitoring >8 years among >1 million people
  • GBS, seizures, syncope, appendicitis, stroke, VTE, autoimmune disorders, anaphylaxis, or congenital abnormalities.

• Serious adverse events very rare with no increased risk among vaccine recipients compared to placebo

• Known side effects: mild fever (1 in 60), discomfort at injection site (1 in 30), and syncope (0.1%)

(CDC, 2013e; CDC, 2013h)
HPV VACCINE RECOMMENDATIONS

Evolution of recommendations for HPV vaccination in the United States

- **Quadrivalent**
  - Routine, females 11 or 12 yrs*
  - and 13-26 yrs not previously vaccinated

- **Quadrivalent or Bivalent**
  - Routine, females 11 or 12 yrs*
  - and 13-26 yrs not previously vaccinated

- **Quadrivalent**
  - May be given, males 9-26 yrs*

- **Quadrivalent**
  - Routine, males 11 or 12 yrs*
  - and 13-21 yrs not previously vaccinated
  - May be given, 22-26 yrs**

- **2006**: Quadrivalent (HPV 6, 11, 16, 18) vaccine; Bivalent (HPV 16, 18) vaccine
- **2007**: Quadrivalent (HPV 6, 11, 16, 18) vaccine; Bivalent (HPV 16, 18) vaccine
- **2008**: Quadrivalent (HPV 6, 11, 16, 18) vaccine; Bivalent (HPV 16, 18) vaccine
- **2009**: Quadrivalent (HPV 6, 11, 16, 18) vaccine; Bivalent (HPV 16, 18) vaccine
- **2010**: Quadrivalent (HPV 6, 11, 16, 18) vaccine; Bivalent (HPV 16, 18) vaccine
- **2011**: Quadrivalent (HPV 6, 11, 16, 18) vaccine; Bivalent (HPV 16, 18) vaccine
- **2012**: Quadrivalent (HPV 6, 11, 16, 18) vaccine; Bivalent (HPV 16, 18) vaccine

* Can be given starting at 9 years of age; ** For MSM and immunocompromised males, quadrivalent HPV vaccine through 26 years of age

HPV9 licensed in December 2014
 Güncellendirilmiş ACIP tavsiyeleri

Age

- Routine vaccination at age 11 or 12 years*
- Vaccination recommended through age 26 for females and through age 21 for males not previously vaccinated
- Vaccination recommended for men through age 26 who have sex with men (MSM) or are immunocompromised (including persons HIV-infected)

*vaccination series can be started at 9 years of age; MMWR 2015;64:300-4
Number of Doses

- Adolescents who receive their 1\textsuperscript{st} dose before age 15 years may complete a 2 dose series:
  - Minimum 5 month interval between 1\textsuperscript{st} and 2\textsuperscript{nd} dose
  - ONLY for younger adolescents

- Adolescents who receive their 1\textsuperscript{st} dose at age 15 years or older must complete the 3 dose series at 0, 1-2 and 6 months

- All adolescents who are immunocompromised must complete the 3 dose series, regardless of age
2 VS 3 DOSES

• 3 dose series (0.1-2, 6): prime, prime, boost
• 2 dose series (0, 6 months): prime, boost

→ Memory B cells need 4-6 months to differentiate into high affinity B cells

• Comparable immune response
  • Immunogenicity higher among younger adolescents

• WHO has recommended 2 dose schedule of HPV vaccine with minimum interval of 6 (up to 12) months if <15 years of age since 2014 → adopted in several countries
HPV VACCINE RATES LOW COMPARED TO OTHER ADOLESCENT VACCINES

National Estimated Vaccination Coverage Levels among Adolescents 13-17 Years, NIS-Teen 2006-2015

MMWR August 2016
CHALLENGES TO HPV VACCINATION

Access
- Adolescents less likely to have medical home
- Missed opportunities
- Vaccine cost / variable insurance coverage
- Identifying eligible patients

Provider Recommendation
- More likely to recommend vaccine to older adolescents
- Vaccine considered optional
- Vaccine safety and efficacy concerns
- Financial Concerns / Reimbursement

Parental Acceptance
- Vaccine safety concerns
- Lack of provider recommendation
- Vaccine not yet necessary: child not sexually active
- Lack of knowledge re: HPV / HPV vaccine

VACCINATE AT EVERY OPPORTUNITY

- Get teens to clinic: Reminder-recall
- Get providers to recommend the vaccine: Decision-support
- Consider alternative locations for vaccine administration
- Standing Orders
- Utilization of electronic health records and registries to identify eligible patients
- Vaccination as recommended at 11-12 years to increase likelihood of regular preventive visits
PUBLIC EDUCATION AND AWARENESS EFFORTS

- Social marketing principles: Product, Price, Place, Promotion to change how vaccines are valued
ADDRESSING BARRIERS: COMMUNICATION

Current Strength of Recommendation in Females, Pediatricians and Family Physicians (N=609)*

- 11-12 yo females: 53 strongly recommend, 37 recommend, but not strongly, 8 recommend, 2 not recommended
- 13-15 yo females: 82 strongly recommend, 15 recommend, but not strongly, 3 recommend, 1 not recommended
- 16-18 yo females: 87 strongly recommend, 10 recommend, but not strongly, 2 recommend, 2 not recommended

PROVIDER RECOMMENDATION MATTERS

• Emphasize adolescent vaccine platform- don’t ‘red flag’ HPV vaccines

• Emphasize message: ‘HPV vaccine is cancer prevention’

• Know the disease and the vaccine so you can provide information to address questions and concerns
RESOURCES AND TOOLS

Tips and Time-savers for Talking with Parents about HPV Vaccine

Recommend the HPV vaccine series the same way you recommend the other adolescent vaccines. For example, you can say "Your child needs these shots today" and name all of the vaccines recommended for the child's age.

Parents may be interested in vaccinating, yet still have questions. Taking the time to listen to parents' questions helps you save time and give an effective response. CDC research shows these straightforward messages work with parents when discussing HPV vaccine—and are easy for you or your staff to deliver.

What Parents Should Know About HPV Vaccine Safety and Effectiveness

HPV vaccines prevent cancer
About 14 million people, including teens, become infected with human papillomavirus (HPV) each year. When HPV infections persist, people are at risk for cancer. Every year, approximately 17,400 women and 9,300 men are affected by cancers caused by HPV. HPV vaccination could prevent many of these cancers.

HPV vaccines are safe
There are two vaccines licensed by the Food and Drug Administration (FDA) and recommended by CDC to protect

HPV vaccine is recommended and safe for boys
One HPV vaccine (Cervarix) is recommended for boys. This vaccine can help prevent boys from getting infected with the HPV-types that can cause cancers of the mouth/throat, penis and anus as well as genital warts.

Like any vaccine or medicine, HPV vaccines might cause side effects
HPV vaccines occasionally cause adverse reactions. The most commonly reported symptoms among females and males are

Give your child a better shot at life — vaccinate for HPV!

www.prevent-hpv.org
ONLINE RESOURCES


• Vaccine Education Center at The Children’s Hospital of Philadelphia (http://www.chop.edu/service/vaccine-education-center/home.html)

• Centers for Disease Control and Prevention: http://www.cdc.gov/vaccines/vpd-vac/hpv/default.htm#clinical

• Immunization Action Coalition: http://www.immunize.org

• Every Child By Two: http://www.ecbt.org

• ACIP Meeting Presentation Slides
  • http://www.cdc.gov/vaccines/acip/meetings

• World Health Organization
  • http://www.who.int/immunization
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• http://www.cdc.gov/flu/about/disease/2014-15.htm#table2


• National, Regional, State, and Selected Local Area Vaccination Coverage Among Adolescents Aged 13–17 Years — United States, 2014. *MMWR*. July 31, 2015 / 64(29);784-792


• Use of Serogroup B Meningococcal Vaccines in Adolescents and Young Adults: Recommendations of the Advisory Council on Immunization Practices, 2015. *MMWR* 64 (41); 1171-6.