Vaccine Update

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Topics

- **Shingles:** The newly licensed vaccine
- **Mumps:** Time for a 3rd dose?
- **Hep B:** New vaccine likely to be licensed soon
- **FluMist:** Will it return to the U.S.?
Shingles:
The newly licensed vaccine
Herpes Zoster: Epidemiology and Disease
Epidemiology

- Annual rate of 4 cases per 1,000.
- About 1 million cases annually in US.
- Lifetime risk of developing HZ is 1 in 3, most commonly in those greater than 65 years of age.
Clinical symptoms: Rash

- Unilateral; typically involves 1-3 adjacent dermatomes.
- Resolves in 5-25 days.
- Occasionally associated with transmission of VZV to susceptible persons.
- A rash involving the ophthalmic branch of the 5th cranial nerve can cause blindness.
A dermatomoral rash caused by herpes-zoster virus
Herpes zoster involvement of the 5th cranial nerve
Clinical symptoms: Pain

- About 90% of episodes associated with pain or discomfort; pain precedes rash in 84% of cases.

- Pain lasts 1-5 days but can last weeks or months (post-herpetic neuralgia or PHN).

- 10-18% of patients will develop PHN. Along with corneal abrasions, low back pain, and labor and delivery, PHN is one of the worst pains in medicine, occasionally leading to suicide.
Herpes Zoster Vaccine: Zostavax
HZ Vaccines

- FDA licensed Zostavax in 2006 based on study of 38,500 non-immunocompromised adults >60 years of age followed for 3 years.

- Zostavax is the live-attenuated Oka strain of VZV (14 times dose in Varivax).

- Efficacy was 51% vs. HZ and 67% vs PHN.

- Local reactions occurred but no serious adverse events.

- 31% of adults >60 have received Zostavax.
## Zostavax: Efficacy vs. HZ

<table>
<thead>
<tr>
<th>Age group (yrs.)**</th>
<th>ZOSTAVAX</th>
<th>Placebo</th>
<th>Vaccine Efficacy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td># subjects</td>
<td># HZ cases</td>
<td>Incidence rate of HZ per 1000 person-yrs.</td>
</tr>
<tr>
<td>Overall</td>
<td>19254</td>
<td>315</td>
<td>5.4</td>
</tr>
<tr>
<td>60-69</td>
<td>10370</td>
<td>122</td>
<td>3.9</td>
</tr>
<tr>
<td>70-79</td>
<td>7621</td>
<td>156</td>
<td>6.7</td>
</tr>
<tr>
<td>≥80</td>
<td>1263</td>
<td>37</td>
<td>9.9</td>
</tr>
</tbody>
</table>

*The analysis was performed on the Modified Intent-To-Treat (MITT) population that included all subjects randomized in the study who were followed for at least 30 days postvaccination and did not develop an evaluable case of HZ within the first 30 days postvaccination.

**Age strata at randomization were 60-69 and ≥70 years of age.
Protective efficacy of Zostavax wanes dramatically
Herpes Zoster Vaccine:
Shingrix (HZ/su)
Strategies used to make Zostavax and Shingrix
**Shingrix (HZ/su)**

- Contains 50 ug of glycoprotein E from VZV plus 2 adjuvants:
  - *QS21*, which contains saponin, a glycoside found in plants.
  - *Monophosphoryl lipid A*, a detoxified lipid A, which was used as an adjuvant in the HPV vaccine Cervarix.

- Licensed by the FDA on October 20, 2017.
The soap bark tree *(Quillaja saponaria)*
QS21 is the 21\textsuperscript{st} peak in chromatography purified product from bark
Shingrix (HZ/su)

- Shingrix is administered in 2 doses intramuscularly at 0 and 2-6 months.
- For prevention of rash, studied in about 28,000 people.
- For prevention of PHN, studied in about 44,000 people.
<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Efficacy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>97.0</td>
</tr>
<tr>
<td>50-59</td>
<td>96.8</td>
</tr>
<tr>
<td>60-69</td>
<td>97.4</td>
</tr>
<tr>
<td>≥70</td>
<td>97.9</td>
</tr>
<tr>
<td>≥80</td>
<td>97.6</td>
</tr>
<tr>
<td>Age (years)</td>
<td>Efficacy (%)</td>
</tr>
<tr>
<td>------------</td>
<td>--------------</td>
</tr>
<tr>
<td>≥50</td>
<td>91.2</td>
</tr>
<tr>
<td>≥60</td>
<td>89.4</td>
</tr>
<tr>
<td>70-79</td>
<td>93.0</td>
</tr>
<tr>
<td>≥80</td>
<td>71.2</td>
</tr>
<tr>
<td>Years post-vaccination</td>
<td>Efficacy (%)</td>
</tr>
<tr>
<td>------------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Year 1</td>
<td>97.6</td>
</tr>
<tr>
<td>Year 2</td>
<td>92</td>
</tr>
<tr>
<td>Year 3</td>
<td>87.9</td>
</tr>
<tr>
<td>Year 4</td>
<td>84.7</td>
</tr>
</tbody>
</table>
HZ/su safety: Local reactions

- Pain: 70-80%
- Erythema: 30-40%
- Swelling: 20-30%
HZ/su safety: Systemic reactions

- Fatigue: 30-50%
- Fever: 10-20%
- Headache: 20-40%
- Myalgia: 30-50%
- Shivering: 10-30%

Fewer than 5% of recipients reported that these symptoms interfered with daily life.
ACIP: Preferential recommendations

- High-dose vs. standard-dose influenza vaccine for older adults (No)
- HPV-4 vs. HPV-2 (No).
- Live attenuated influenza vaccine (FluMist) versus inactivated influenza vaccine for children (Yes).
- IPV versus OPV (Yes).
- DTaP versus DTP (Yes).
ACIP recommended HZ/su for vaccination of immunocompetent adults 50 years and older.

ACIP recommended HZ/su for individuals previously vaccinated with Zostavax.

ACIP gave a preferential recommendation for HZ/su over Zostavax.
ACIP: October 25, 2017

- ACIP gave a preferential recommendation for HZ/su over Zostavax by a vote of 8-7.

- Concerns about the safety of the novel adjuvant, QS21. If safety is later an issue, likely that Zostavax will no longer be available. Have we done more harm than good?

- Question is not when do you know everything but when do you know enough.
Mumps vaccine:
Time for a 3rd dose?
Mumps pre-vaccine era (1917-1967)

- Peak incidence in 5-9 year olds.
- About 90% of children infected by age 14.
- Most cases late winter, early spring.
- Adult outbreaks in the military.
Mumps vaccine

- Licensed in 1967.
- Live attenuated strain (Jeryl Lynn), genotype A.

- Effectiveness estimates:
  - One Dose: 77% (CI 49-88)
  - Two Doses: 88% (CI 66-95)

- Unlike measles and rubella, immunity to mumps fades 10 years after 1\textsuperscript{st} or 2\textsuperscript{nd} dose.
Reported Mumps Cases, United States, Vaccine Era, 1968-2016

1977 1st Dose ACIP Recommendation

1989 2nd Dose MMR ACIP Recommendation

2006 Midwest Outbreak

2009 Northeast Outbreak

2016 Arkansas Outbreak

Source: National Notifiable Diseases Surveillance System (passive surveillance); 2016 data is preliminary (May 31, 2017) and subject to change.
### Mumps Cases, Incidence Rate (IR) and Outbreak (OB)-Related Data, United States, 2011-2016

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td><strong>Case Count</strong></td>
<td>404</td>
<td>229</td>
<td>584</td>
<td>1223</td>
<td>1329</td>
<td>6353</td>
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<tr>
<td><strong>I.R.</strong></td>
<td>1.3</td>
<td>0.7</td>
<td>1.9</td>
<td>3.8</td>
<td>4.2</td>
<td>19.9</td>
</tr>
<tr>
<td><strong>OB Cases</strong></td>
<td>128</td>
<td>3</td>
<td>313</td>
<td>747</td>
<td>836</td>
<td>4975</td>
</tr>
<tr>
<td><strong>% of OB Cases</strong></td>
<td>32</td>
<td>1.3</td>
<td>54</td>
<td>61</td>
<td>63</td>
<td>78</td>
</tr>
<tr>
<td><strong>Jurisdictions w/ OB cases</strong></td>
<td>9</td>
<td>3</td>
<td>11</td>
<td>15</td>
<td>14</td>
<td>32</td>
</tr>
</tbody>
</table>

Source: National Notifiable Disease Surveillance System (passive surveillance); 2016 and 2017 data is preliminary (as of May 31, 2017) and subject to change; data provided by Nakia Clemmons (CDC)
Characteristics of Reported Mumps Cases and Outbreaks, United States, 2017*

- Highest incidence: 18-22 age group
- Age: median=23 years, IQR=15-30 years
- Vaccination status: 73% ≥2 MMR doses
- Outbreaks: at least 40 known to CDC
  - 19 universities
  - 14 community-wide (9 in close-knit communities [8 in Marshallese communities])
  - 7 other close contact settings: prison [3], high school [2], military facility [1], hockey team [1]

Reported Mumps Incidence Rates by Year and Age Group, United States, 2011-2017

Source: National Notifiable Disease Surveillance System (passive surveillance); 2016 and 2017 data is preliminary (as of May 31, 2017) and subject to change; data provided by Nakia Clemmons (CDC)
Factors that Might Contribute to the Increasing Number of Mumps Outbreaks

- Vaccine effectiveness:
  - 2 doses: median 88% (range 53%-95%)

- Waning of vaccine-induced immunity: serologic and epidemiologic evidence

- Increase in number of mumps outbreaks

- Other factors?

- Antigenic differences circulating vs. vaccine strains

- Force of infection

Factors presented at the February 2017 ACIP meeting
Arguments for a 3\textsuperscript{rd} dose recommendation

\begin{itemize}
  \item Memory responses to mumps poorer than for measles or rubella following MMR.
    \begin{itemize}
      \item For rubella, 5,000 memory B cells per 10\textsuperscript{6} cells
      \item For measles, 3,000 memory B cells per 10\textsuperscript{6} cells
      \item For mumps, 300 memory B cells per 10\textsuperscript{6} cells
    \end{itemize}
  \item Could reasonably argue for 3-dose recommendation for people more than 10 years post 2\textsuperscript{nd} dose who are in an outbreak situation.
\end{itemize}
Mumps outbreak: University of Iowa

- Recent study of effectiveness of a 3rd dose of mumps vaccine during an outbreak at the University of Iowa.
- Of 20,496 university students enrolled during the 2015-2016 academic year, 259 were diagnosed with mumps.
- Before the outbreak, 98.1 percent of students had received 2 doses of MMR.

Mumps outbreak: University of Iowa

- During the outbreak, 4,783 received a 3rd dose of MMR.
- The attack rate was lower among those who had received a 3rd dose of MMR than among those who hadn’t (6.7 vs. 14.5 cases per 1,000 population, \( P < 0.001 \)).

Students who had received MMR vaccine 13 or more years prior to the outbreak had at least a 9-fold greater risk of mumps than those who had received MMR more recently.

The authors concluded: “The campaign to administer a 3rd dose of MMR vaccine improved mumps outbreak control and waning immunity contributed to the outbreak.”

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Pre-</th>
<th>Post-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orchitis</td>
<td>30%</td>
<td>4.3%</td>
</tr>
<tr>
<td>Oophoritis</td>
<td>5%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Mastitis</td>
<td>30%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Hearing loss</td>
<td>4%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Aseptic men.</td>
<td>1-15%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>4%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Encephalitis</td>
<td>0.03-0.5%</td>
<td>0.02%</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>5.5%</td>
<td>0.8%</td>
</tr>
</tbody>
</table>
“Persons previously vaccinated with two doses of mumps-containing vaccine who were identified by public health as being at increased risk for mumps because of an outbreak should receive a 3rd dose of mumps-containing vaccine to improve protection against mumps and its complications.”

Argument made during the meeting to give MMR at entrance to college rather than waiting for an outbreak.
Hepatitis B vaccine: New vaccine likely to be licensed soon
The first hepatitis B vaccine
Hepatitis B Particle Types

- Pre S1 Domain
- Pre S2 Domain
- S Domain
- HBc Genome Polymerase

Hepatitis B Virion (a.k.a. Dane Particle)
Secreted Filament
Secreted Sphere
Electron micrograph from a patient infected with hepatitis B virus
The first hepatitis B vaccine

- Maurice Hilleman took plasma from people infected with hepatitis B virus and purified hepatitis B surface antigen particles.
- Preparation was subjected to treatment with pepsin, urea, and formaldehyde.
- Used in U.S. between 1981 and 1986 and targeted to high-risk groups.
- Enthusiasm limited by source of HBsAg in the vaccine (human blood).
The second hepatitis B vaccine
Recombinant HBV Vaccine Production

The steps involved in preparing a recombinant DNA hepatitis B vaccine in yeast.
The second hepatitis B vaccine

- Recommended for all newborns in the United States as a three-dose vaccine to be given at birth, 1-2 months, and 6-15 months.

- Adherence to this schedule has virtually eliminated hepatitis B virus infections in children.

- But problems remain: (1) about 5 percent of recipients don’t respond; (2) the vaccine is less effective in certain high-risk groups (diabetes, renal disease, immunosuppressed, obese, elderly, smokers).
The third hepatitis B vaccine
Heplisav
Hepatitis B vaccine, recombinant
The third hepatitis B vaccine

- Contains 20 micrograms of recombinant-derived hepatitis B surface antigen combined with 3 milligrams of a novel CpG-oligonucleotide adjuvant.

- CpG are short, single-stranded, synthetic, DNA molecules containing cytosine (C) and guanine (G) linked by a phosphodiester (p).

- Given as a 2-dose instead of 3-dose vaccine.

- Licensure expected on November 9, 2017 for use in adults over 18 years of age.
Adults recommended to receive hepatitis B vaccine

- Household and sexual contacts of HBsAg-positive people.
- Injection drug users.
- Healthcare and public safety personnel.
- Hemodialysis patients.
- International travelers to region with high or intermediate endemicity.
- Persons with chronic liver disease.
- Persons with HIV infection.
- Adults with type-1 diabetes.
CpG-oligonucleotide adjuvants

- CpG motifs are considered to be pathogen-associated molecular patterns (PAMPs) due to their abundance in microbial genomes but rarity in vertebrate genomes.
- The CpG PAMP is recognized by our innate immune system through toll-like receptors (TLRs) on B cells and dendritic cells.
- TLRs recognize structurally conserved molecules from microbes.
Ligands for TLRs

- Lipoproteins
- Lipoarabinomannan
- LPS (Leptospira)
- LPS (P. gingivalis)
- PGN (Gram-positive)
- Zymosan (Yeast)
- GPI anchor (T. cruzi)
- LPS (Gram-negative)
- Taxol (Plant)
- F protein (RS virus)
- hsp60 (Host)
- Fibronectin (Host)
- Flagellin
- CpG DNA

TLR2 or TLR6
TLR4
TLR5
TLR9
Heplisav-B studies

- Studied in about 14,000 adults vs. Engerix.
- Protective efficacy predicted by antibody responses $\geq 10$ mIU/ml of HBsAb.
- Overall seroprotection rate was 95% for Heplisav and 81.2% for Engerix at week 28 and 90.1% vs. 70.8% at week 32.
- In patients with type 2 diabetes, seroprotection rate was 90% for Heplisav and 65.1% for Engerix.
<table>
<thead>
<tr>
<th>Years</th>
<th>Heplisav-B</th>
<th>Engerix</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-29</td>
<td>100%</td>
<td>93.9%</td>
</tr>
<tr>
<td>30-39</td>
<td>98.9%</td>
<td>92%</td>
</tr>
<tr>
<td>40-49</td>
<td>97.2%</td>
<td>84.2%</td>
</tr>
<tr>
<td>50-59</td>
<td>95.2%</td>
<td>79.7%</td>
</tr>
<tr>
<td>60-70</td>
<td>91.6%</td>
<td>72.6%</td>
</tr>
</tbody>
</table>
## Heplisav-B vs. Engerix safety

<table>
<thead>
<tr>
<th>Local</th>
<th>Heplisav-B</th>
<th>Engerix</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>41.7%</td>
<td>40.8%</td>
</tr>
<tr>
<td>Redness</td>
<td>3.7%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Swelling</td>
<td>2.4%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Systemic</td>
<td>Heplisav-B</td>
<td>Engerix</td>
</tr>
<tr>
<td>------------------------</td>
<td>------------</td>
<td>---------</td>
</tr>
<tr>
<td>Fatigue</td>
<td>21.4%</td>
<td>25.1%</td>
</tr>
<tr>
<td>Headache</td>
<td>20.1%</td>
<td>25.3%</td>
</tr>
<tr>
<td>Malaise</td>
<td>13.8%</td>
<td>16%</td>
</tr>
<tr>
<td>Fever ≥38.0°C</td>
<td>1.7%</td>
<td>3.4%</td>
</tr>
<tr>
<td>Acute MI</td>
<td>0.17%</td>
<td>0.05%</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>0.04%</td>
<td>0.18%</td>
</tr>
</tbody>
</table>
Heplisav-B results in high levels of seroprotection.

Heplisav-B two dose series administered at 0 and 1 month will likely improve series completion.

Most safety outcomes similar between Heplisav-B and Engerix.

Acute MI was reported to be higher in Heplisav-B group; safety will be monitored in post-marketing studies.
FluMist: Will it return to the U.S.?
What is FluMist?
LAIV

- Made using two influenza viruses (A/Ann Arbor/6/60 and B/Ann Arbor/1/66) that were cold-temperature adapted in the 1960s.

- HA and NA of circulating strains to be included in the vaccine are reassorted into these two viruses.
Attenuated Donor Master Strain

Attenuated Vaccine Strain: Coat of Virulent strain with Virulence Characteristics of Attenuated Strain

New Virulent Antigenic Variant Strain
If LAIV is available, it should be used for healthy children aged 2 through 8 years who have no contraindications or precautions.

If LAIV is not immediately available, IIV should be used. Vaccination should not be delayed in order to procure LAIV.
Why did the ACIP give LAIV a preferential recommendation in 2014?
Pre-licensure studies showed that LAIV was more effective than IIV
LAIV vs IIV

LAIV vs IIV efficacy for lab-confirmed influenza regardless of match between vaccine and circulating strains.

<table>
<thead>
<tr>
<th>Study</th>
<th>Incidence of influenza</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LAIV</td>
</tr>
<tr>
<td>Study 1</td>
<td>3.9%</td>
</tr>
<tr>
<td>Study 2</td>
<td>2.8%</td>
</tr>
<tr>
<td>Study 3</td>
<td>4.5%</td>
</tr>
</tbody>
</table>
LAIV vs IIV

◆ Study 1:
  Belshe, NEJM (2007); 356:685-96

◆ Study 2:
  Ashkenazi, Ped Infect Dis J (2006); 25:870-9

◆ Study 3:
  Fleming, Ped Infect Dis J (2006); 25:860-9
Before June 2014, ACIP had not expressed a preference for LAIV over IIV. But other countries and some US states had already expressed a preference for LAIV:

- Canada 2-17 years
- United Kingdom 2-17 years
- Israel 2-17 years
- Germany 2-6 years
- US-Oregon 2-5 years
- US-Washington 2-7 years
So what happened?
US Flu VE Network:
IIV outperformed LAIV during the 2015-2016 season
LAIV and IIV vaccine effectiveness ages 2–8 years, by influenza type/subtype, 2015-16

<table>
<thead>
<tr>
<th></th>
<th>Any influenza</th>
<th>H1N1pdm09</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted Vaccine Effectiveness (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAIV4</td>
<td>58</td>
<td>62</td>
<td>36</td>
</tr>
<tr>
<td>IIV3/4</td>
<td>58</td>
<td>47</td>
<td>83</td>
</tr>
</tbody>
</table>

| Total, Flu +  | 183           | 213       | 113     |
| Vaccinated, Flu + | 28           | 58        | 20      |
Why?
H1N1 didn’t replicate well enough to induce a protective immune response
US Flu VE Network: LAIV and IIV VE age 2-17 yrs
Any Influenza A or B

<table>
<thead>
<tr>
<th>Year</th>
<th>LAIV3</th>
<th>IIV3</th>
<th>LAIV3</th>
<th>IIV3</th>
<th>LAIV3</th>
<th>IIV3</th>
<th>LAIV3</th>
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<th>LAIV3</th>
<th>IIV3</th>
<th>LAIV3</th>
<th>IIV3</th>
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<tbody>
<tr>
<td>2010-11</td>
<td>267</td>
<td>314</td>
<td>225</td>
<td>264</td>
<td>722</td>
<td>859</td>
<td>220</td>
<td>222</td>
<td>588</td>
<td>562</td>
<td>324</td>
<td>367</td>
</tr>
<tr>
<td>Mixed</td>
<td>71</td>
<td>71</td>
<td>67</td>
<td>55</td>
<td>46</td>
<td>45</td>
<td>60</td>
<td>-1</td>
<td>3</td>
<td>15</td>
<td>3</td>
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<td>H3N2</td>
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<td>-1</td>
<td>3</td>
<td>15</td>
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<td>H3N2</td>
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<td>55</td>
<td>-1</td>
<td>3</td>
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<td>H1N1</td>
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<td>H3N2</td>
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<td>63</td>
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</tbody>
</table>

Total, Flu +

Vaccinated, Flu +
On February 24, 2016, the ACIP withdrew its recommendation.
Option B: Interim Recommendation That LAIV Should Not Be Used

“In light of the evidence for poor effectiveness of LAIV in the U.S. over the last three influenza seasons (2013-14 through 2015-16), for the 2016-17 season, ACIP makes the interim recommendation that LAIV should not be used.”
LAIV

- Company has replaced H1N1pdm009 with H1N1/A/Slovenia.
- A/Slovenia has improved replication in human nasal epithelium.
- A/Slovenia induces protection in ferret model.
- FluMist used during 2016-2017 season in Japan, UK, Canada, and Germany had comparable efficacy to IIV (but H3N2 season).
Additional Resources

- ACIP meetings on-line
  - http://www.cdc.gov/vaccines/recs/acip/default.htm
- Vaccine Education Center at CHOP
  - http://vaccine.chop.edu
- Centers for Disease Control and Prevention
  - http://www.cdc.gov/vaccines
- Immunization Action Coalition
  - http://www.immunize.org
- Every Child By Two
  - http://www.ecbt.org
To obtain continuing education credits, go to:

http://vaccine.chop.edu/credits