Vaccine Controversies: Pertussis, Pneumococcal and Zoster vaccines

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Alameda County Immunization Update
2015
Pertussis Vaccines: Solution or problem (or both)?
Pertussis Vaccines

• Whole cell: First licensed in 1914. DTP in 1948.
  • Suspensions of killed organisms.
  • Widespread use coincided with large decreases in pertussis
• 1990’s: due to safety concerns Acellular vaccines (DTaP) replaced all childhood DTP in the US
• US: 5 doses of DTaP (2, 4, 6, 12 months and 4-6 years).
• 2006: Tdap for adolescents and adults X 1
Figure 2. Number and incidence of reported pertussis cases by year of onset -- California, 1946-2014*

*Includes cases reported to CDPH as of 2/12/2015
2010: Pertussis outbreak in California

KP Pertussis rates with acellular vaccination history
By age in years in 2010

% vaccinated with acellular vaccines as infants.
Acellular vaccines are less protective than older whole cell vaccines
DTaP wanes on average 42% per year after immunization.
Tdap vaccine is 64% effective at preventing PCR-confirmed pertussis in the first 2 years.
Tdap Waning Effectiveness  
(Not yet published)

<table>
<thead>
<tr>
<th></th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual Tdap Waning</td>
<td>1.37 (1.22-1.55)</td>
</tr>
</tbody>
</table>

➢ Tdap VE wanes 37% per year on average.
Vaccine Effectiveness

Tdap waning

Average VE 64% (first 2 years)
So what’s happened with pertussis since 2010?
PCR-confirmed pertussis rates
By age in years
This drop attributed to 65% initial Tdap effectiveness

This rise attributed to Tdap waning 37% each year
Summary

• Acellular vaccines are not as effective as older, whole cell vaccines

• Acellular vaccine effectiveness wanes each year after immunization, so the effect only lasts 3-5 years.

• Use of these vaccines will not prevent outbreaks, and is probably contributing to the resurgence of pertussis.
Pertussis controversies

• Should we use Tdap more? Or less?
• Can we prevent outbreaks?
• Do we need a different schedule, or
• Do we need a better vaccine?
Reminder: Tdap is

• Recommended for every pregnancy
  – To prevent illness in infants, in whom pertussis is the most deadly
  – Appears safe and effective
  – Antibodies are higher in neonates than moms
  – Only slight interference with primary series in infant
Next topic

• Are all pneumococcal vaccines the same?
Antibody responses to Polysaccharide antigens

- B cells are activated in the lymph nodes
- No T cell activation
  - Do not trigger Germinal Centers
  - Brief antibody responses
  - No immune memory
  - No boosting
Repeat Polysaccharide Vaccination may produce Hypo-responsiveness.

**First dose**

**Repeat Dose**
But...Add a Protein conjugate to the Polysaccharide...

Conjugate A  Conjugate C  Conjugate W  Conjugate Y
Protein antigen (or adjuvant):

- The DC is activated by the innate immune system
- Now, when the antigen is presented, **Both B cells and T cells are stimulated**
- You get a much greater immune response
- More like an actual infection
Induction of Memory Cells: polysaccharide vs. conjugate

Boosting: reactivation of memory cells

- Comparison of primary and booster Ab responses to protein-containing vaccines
Compared to primary antibody responses, Booster responses are:

- Faster (peak ~ at day 7)
- Higher antibody titers
- More prolonged (years)
- “Stronger”: Higher neutralizing capacity (increased affinity).
Prevnar vs Pneumovax

- **Prevnar13**: 13 serotypes conjugated to a diphtheria protein
- **Pneumovax**: 23 serotypes, all polysaccharide antigens, no conjugate
# 2 pneumococcal vaccines

<table>
<thead>
<tr>
<th>Activity</th>
<th>Pneumovax</th>
<th>Prevnar</th>
</tr>
</thead>
<tbody>
<tr>
<td>Booster response</td>
<td>No (may cause hypo-responsiveness)</td>
<td>Yes</td>
</tr>
<tr>
<td>Prevent IPD in children</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Prevent IPD in adults</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Prevent pneumonia</td>
<td>No</td>
<td>yes</td>
</tr>
</tbody>
</table>
## ACIP recommendations

<table>
<thead>
<tr>
<th>Group</th>
<th>Vaccine Schedule</th>
<th>Booster?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants</td>
<td>PCV13 at 2, 4, 6 and 12 months</td>
<td>yes</td>
</tr>
<tr>
<td>Healthy adults</td>
<td>none</td>
<td>no</td>
</tr>
<tr>
<td>Adults 65 years and older</td>
<td>PCV13</td>
<td>no</td>
</tr>
<tr>
<td>Immunocompromised adults</td>
<td>PCV13</td>
<td>Yes, with PPSV23</td>
</tr>
<tr>
<td>Adults with non-immunocompromising conditions</td>
<td><strong>PPSV23</strong></td>
<td>PCV13 at 65 years</td>
</tr>
</tbody>
</table>

*PPSV23* indicates a pneumococcal polysaccharide vaccine.
Pneumococcal controversy

• Should we ever use PPSV23 first, or should we focus on vaccines that can prime and boost?
  – How important is hypo-responsiveness?
• Will the conjugated vaccine help adults in a world where infants are already protected?
  – ACIP will review in 3 years
Speaking of priming and boosting...
Can only Proteins add this effect?

- Toxoids
- Live vaccines
- Adjuvants

- All of these can stimulate the innate immune system
How can Adjuvants Enhance Antibody Responses?

1. Increase Ag delivery to DCs and B cells
2. Activate DCs and T cells
3. Increase Germinal center responses
4. Activate TLRs
5. Enhance memory
Current FDA-licensed adjuvants

Alum (aluminum)

- DTP
- DTaP
- Hib (*Haemophilus influenzae* type b) conjugate vaccines
- Pneumococcal conjugate vaccine
- Hepatitis B vaccines
- Hepatitis A vaccines
- Human Papillomavirus vaccine
- Rabies vaccine
Other Adjuvants

- Emulsions (slow-release)
  - MF59
- Nucleic Acid-derived
  - CPG
- Microparticles
  - VLPs, microspheres
- Microorganism derived
  - LPS (MPL)
- Tensioactive compounds
  - Saponin
MPL: Monophosphoryl Lipid A

- Derivative of lipopolysaccharide (LPS) of Salmonella
  - Modified for reduced toxicity
- Used in GSK’s Cervarix® HPV vaccine
- Licensed in Europe for Hepatitis B (GSK-Fendrix®)
- Activates TLR4
QS21 adjuvant

- *From Quillaja saponaria (Soap Bark tree)* native to Chile

- Purified saponin derivative
- Used in over 60 trials
- Very reactogenic
Transition page...

- We’ll return to adjuvants shortly
Shingles (Zoster) vaccines

• How well do they work?
• Do they last?
• Are they worth it?
Zostavax™

- Live attenuated varicella vaccine
- 14 times the dose in Varivax™
- Safe, well-tolerated
Live vaccines

• Generally considered more potent and durable than killed
  – Yellow fever, MMR
• Don’t require adjuvants
Vaccine Study Center research

• presented to ACIP 5/11/2015

<table>
<thead>
<tr>
<th>Age at vaccination</th>
<th>VE</th>
<th>P-value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccinated at 50-59 years*</td>
<td>63.9%</td>
<td>&lt;0.001</td>
<td>(54.5, 71.4)</td>
</tr>
<tr>
<td>Vaccinated at 60-69 years</td>
<td>51.1%</td>
<td>&lt;0.001</td>
<td>(48.6, 53.4)</td>
</tr>
<tr>
<td>Vaccinated at 70-79 years</td>
<td>45.3%</td>
<td>&lt;0.001</td>
<td>(42.2, 48.3)</td>
</tr>
<tr>
<td>Vaccinated at 80+ years</td>
<td>46.2%</td>
<td>&lt;0.001</td>
<td>(40.6, 51.3)</td>
</tr>
</tbody>
</table>

*50-59 starting in 2011

VE was estimated for the first episode of herpes zoster during follow-up. Abbreviations: VE denotes vaccine effectiveness, CI confidence interval, IC immunocompromised, DxCG diagnostic cost groups, HCUP healthcare cost and utilization project.
### Zostavax vaccine effectiveness over time

Adjusted for calendar time, age, sex, race or ethnic group, flu vaccination, IC status at risk, outpatient utilization, DxCG score, and HCUP risk score

<table>
<thead>
<tr>
<th>Zostavax vaccination status</th>
<th>VE</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccinated 30 days to &lt; 1 year</td>
<td>68.8%</td>
<td>66.4% – 71.1%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Vaccinated 1 to &lt; 2 years</td>
<td>45.1%</td>
<td>41.5% – 48.5%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Vaccinated 2 to &lt; 3 years</td>
<td>37.9%</td>
<td>33.3% – 42.2%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Vaccinated 3 to &lt; 4 years</td>
<td>41.0%</td>
<td>36.0% – 45.6%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Vaccinated 4 to &lt; 5 years</td>
<td>38.0%</td>
<td>31.8% – 43.6%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Vaccinated 5 to &lt; 6 years</td>
<td>32.4%</td>
<td>24.0% – 39.9%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Vaccinated 6 to &lt; 7 years</td>
<td>24.1%</td>
<td>6.4% – 38.5%</td>
<td>0.010</td>
</tr>
</tbody>
</table>

VE was estimated for the first episode of herpes zoster during follow-up. VE was calculated as 1-hazard ratio. Abbreviations: VE denotes vaccine effectiveness, CI confidence interval, IC immunocompromised, DxCG diagnostic cost groups, HCUP healthcare cost and utilization project.
Here’s something new

The NEW ENGLAND JOURNAL of MEDICINE

Efficacy of an Adjuvanted Herpes Zoster Subunit Vaccine in Older Adults

Published online on April 28, 2015 at NEJM.org.
GSK’s adjuvanted Shingles Vaccine – Not yet licensed

<table>
<thead>
<tr>
<th>Cohort and Age Group</th>
<th>No. of Participants</th>
<th>Vaccine Efficacy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number</td>
<td>7698</td>
<td>96.2% (92.7–98.3)</td>
</tr>
<tr>
<td>50–59 yr</td>
<td>3645</td>
<td>96.9% (90.6–99.4)</td>
</tr>
<tr>
<td>60–69 yr</td>
<td>2244</td>
<td>94.1% (85.6–98.1)</td>
</tr>
<tr>
<td>70 yr or older</td>
<td>1809</td>
<td>98.3% (89.9–100.0)</td>
</tr>
</tbody>
</table>
How can it be so potent?

- Adjuvants: remember these?
  - MPL
  - QS21
### Is it safe? Table 3. Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>HZ vaccine Group</th>
<th>Placebo Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% affected (95% CI)</td>
<td>% affected (95% CI)</td>
</tr>
<tr>
<td><strong>Injection-site reactions</strong></td>
<td>81.5 (80.3–82.6)</td>
<td>11.9 (11.0–12.9)</td>
</tr>
<tr>
<td>Pain</td>
<td>79.1 (77.8–80.2)</td>
<td>11.2 (10.3–12.2)</td>
</tr>
<tr>
<td>Redness</td>
<td>38.0 (36.5–39.4)</td>
<td>1.3 (1.0–1.7)</td>
</tr>
<tr>
<td>Swelling</td>
<td>26.3 (25.0–27.6)</td>
<td>1.1 (0.8–1.4)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>9.5 (8.7–10.4)</td>
<td>0.4 (0.2–0.6)</td>
</tr>
<tr>
<td><strong>Systemic reactions</strong></td>
<td>66.1 (64.7–67.6)</td>
<td>29.5 (28.2–30.9)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>46.3 (44.8–47.8)</td>
<td>12.1 (11.2–13.1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>45.9 (44.4–47.4)</td>
<td>16.6 (15.5–17.8)</td>
</tr>
<tr>
<td>Headache</td>
<td>39.2 (37.8–40.7)</td>
<td>16.0 (14.9–17.1)</td>
</tr>
<tr>
<td>Shivering</td>
<td>28.2 (26.8–29.5)</td>
<td>5.9 (5.2–6.7)</td>
</tr>
<tr>
<td>Fever</td>
<td>21.5 (20.3–22.7)</td>
<td>3.0 (2.5–3.6)</td>
</tr>
<tr>
<td>GI symptoms</td>
<td>18.0 (16.9–19.2)</td>
<td>8.8 (8.0–9.7)</td>
</tr>
<tr>
<td>Grade 3 systemic reaction</td>
<td>11.4 (10.5–12.4)</td>
<td>2.4 (2.0–2.9)</td>
</tr>
<tr>
<td><strong>Serious adverse events</strong></td>
<td>9.0 (8.3–9.6)</td>
<td>8.9 (8.3–9.6)</td>
</tr>
<tr>
<td>Immune diseases</td>
<td>1.0 (0.8–1.3)</td>
<td>1.3 (1.0–1.5)</td>
</tr>
<tr>
<td>Death</td>
<td>2.2 (1.9–2.5)</td>
<td>2.3 (1.9–2.6)</td>
</tr>
</tbody>
</table>
Zoster controversy

- Would you rather have a more potent vaccine that has more side effects?
- Should people wait for the new one (up to 2 years)?
That’s all!

Questions?