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Duke University and Durham VA Medical Centers
Zoster Vaccines in Older Adults
September 21, 2017
The Clinical Problem . . .

- 78 year old man in good health working as the CEO of a company . . .
In the Patient’s Words

I’ve had postherpetic neuralgia for . . . from the start of the shingles until now, I don’t know, it’s been 50 some days. The pain has worn me down to the last straw. I am at the end of my line. I got to have somebody do something. I desperately, desperately need help. I don’t know how much longer I can take it.
Pain is the Cardinal Problem Posed by Herpes Zoster in Older Adults -- *Acute and Chronic Pain*

Acute and Postherpetic Neuralgia
Adverse Impact on Multiple Domains of Health

<table>
<thead>
<tr>
<th>Physical</th>
<th>Psychological</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Fatigue</td>
<td>• Depression</td>
</tr>
<tr>
<td>• Anorexia</td>
<td>• Anxiety</td>
</tr>
<tr>
<td>• Weight loss</td>
<td>• Difficulty concentrating</td>
</tr>
<tr>
<td>• Physical inactivity</td>
<td></td>
</tr>
<tr>
<td>• Insomnia</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Social</th>
<th>Functional</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Decreased social gatherings</td>
<td>• Interfere with basic and</td>
</tr>
<tr>
<td>• Change in social role</td>
<td>instrumental activities of daily</td>
</tr>
<tr>
<td></td>
<td>living</td>
</tr>
<tr>
<td></td>
<td>– Dressing, Bathing, Eating,</td>
</tr>
<tr>
<td></td>
<td>Mobility</td>
</tr>
<tr>
<td></td>
<td>– Travelling, Cooking,</td>
</tr>
<tr>
<td></td>
<td>Housework, Shopping</td>
</tr>
</tbody>
</table>

Electron Micrograph of Varicella Zoster Virus (VZV)
Age and Incidence of Herpes Zoster

Kawai et al. BMJ Open 2014;4:e004833
Strategies to Enhance Protection of Older Adults Against Vaccine-Preventable Diseases

• Improve Immune Response to Vaccines
  – **Live, attenuated**
  – **Higher dose**
  – Adjuvants
  – Conjugates
  – Subunit
  – DNA
  – Recombinant vector

[Link: https://www.vaccines.gov/more_info/types]
Live Attenuated Zoster Vaccine

- Live, attenuated, cell-free preparation of Oka/Merck strain VZV
- Contains whole live virus, viral antigen and
- Neomycin, sucrose, gelatin, glutamate, inorganic salts

- Formulated to contain substantially more live virus and viral antigen than are contained in the varicella vaccine

www.cdc.gov/mmwr/preview/mmwrhtml/rr5705a1.htm
Shingles Prevention Study

• **Design:** Randomized, double-blind, placebo-controlled, stratified by age, 60-69 and ≥ 70 years

• **Setting:** 22 US sites (16 VA and 6 university medical centers)

• **Participants:** 38,546 immunocompetent adults ≥60 years old
  – 19,270 zoster vaccine
  – 19,276 placebo

Shingles Prevention Study

- **Intervention:** One dose of live attenuated zoster vaccine or placebo
- **Outcomes:** Incidence of HZ and PHN and Pain Burden of Illness (BOI)

Incidence of herpes zoster (per 1000 person years)

- All Subjects: 11.1%
- Age 60–69: 10.7%
- ≥70: 11.5%

Efficacy of Live Zoster Vaccine

- Placebo: 51.3% (44.2-57.6)
- Zoster Vaccine Live: 63.9% (55.5-70.9)
- ≥70: 37.6% (25.0-48.1)

Efficacy of Live Zoster Vaccine
Incidence of Postherpetic Neuralgia

Efficacy (95% CI)
66.5% (47.5-79.2) 65.7% (20.4-86.7) 66.8% (43.3-81.3)

Incidence of PHN (per 1000 person years)

Figures 1 and 2 should be read with the footnotes that contain important general information and considerations for special populations.

Figure 1. Recommended immunization schedule for adults aged 19 years or older by age group, United States, 2017

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>19–21 years</th>
<th>22–26 years</th>
<th>27–59 years</th>
<th>60–64 years</th>
<th>≥ 65 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 dose annually</td>
</tr>
<tr>
<td>Td/Tdap</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Substitute Tdap for Td once, then Td booster every 10 yrs</td>
</tr>
<tr>
<td>MMR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 or 2 doses depending on indication</td>
</tr>
<tr>
<td>VAR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 doses</td>
</tr>
<tr>
<td>HZV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 dose</td>
</tr>
<tr>
<td>HPV–Female</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3 doses</td>
</tr>
<tr>
<td>HPV–Male</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3 doses</td>
</tr>
<tr>
<td>PCV13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 dose</td>
</tr>
<tr>
<td>PPSV23</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 dose</td>
</tr>
<tr>
<td>HepA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 or 3 doses depending on vaccine</td>
</tr>
<tr>
<td>HepB</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3 doses</td>
</tr>
<tr>
<td>MenACWY or MPSV4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 or more doses depending on indication</td>
</tr>
<tr>
<td>MenB</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 or 3 doses depending on vaccine</td>
</tr>
<tr>
<td>Hib</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 or 3 doses depending on indication</td>
</tr>
</tbody>
</table>

- **Recommended for adults who meet the age requirement, lack documentation of vaccination, or lack evidence of past infection**
- **Recommended for adults with additional medical conditions or other indications**
- **No recommendation**
Effect of Zoster Vaccine on Incidence of Herpes Zoster in Persons 50-59 Years Old

Efficacy (95% CI) 69.8% (54.1-80.6)

<table>
<thead>
<tr>
<th>Incidence of herpes zoster (per 1000 person years)</th>
<th>10</th>
<th>8</th>
<th>6</th>
<th>4</th>
<th>2</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>6.60</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>11,228</td>
</tr>
<tr>
<td>Zoster Vaccine</td>
<td>1.99</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>11,211</td>
</tr>
</tbody>
</table>

How Persistent is the Effect of the Live Zoster Vaccine?

VA CSP #403B: The Short-Term Persistence Substudy*

- Follow-up 3.3 to 7.8 years
- Comparator: Placebo
- Vaccine Efficacy for HZ: 39.6%

VA CSP #403C: The Long-Term Persistence Substudy**

- Follow-up 4.7 to 11.6 years
- Comparator: Historical controls
- Vaccine Efficacy for HZ: 21%

Efficacy of Live Zoster Vaccine on Herpes Zoster by Year After Vaccination

SPS = Shingles Prevention Study; STPS = Short-Term Persistence Substudy; LTPS = Long-Term Persistence Substudy

So . . . What about a booster dose?

- Live zoster vaccine administered as a booster dose ≥10 years after first dose in individuals ≥70 years old
  - Significantly increases immunity to VZV
  - Increase in VZV immunity in the booster dose group is significantly higher than matched first-time immunization group for one year after immunization
- But clinical significance of immunological findings is unknown . . .
  - ACIP does not recommend a second dose of live zoster vaccine at this time
Strategies to Enhance Protection of Older Adults Against Vaccine-Preventable Diseases

• Improve Immune Response to Vaccines
  – Live, attenuated
  – Higher dose
  – **Adjuvants**
  – **Subunit**
  – Conjugates
  – DNA
  – Recombinant vector

http://www.vaccines.gov/more_info/types
An adjuvant is a substance that potentiates the immune response to an antigen.

Rapid response to pathogens (e.g. post-exposure prophylaxis)

Vaccine response broadening (influenza, HIV, malaria)

Dose sparing (use less antigen, increase global vaccine supply)

Reduced number of immunizations

New T cell vaccines (TB, viral, etc.)

Therapeutic vaccines (HPV, cancer, etc.)

New adjuvants

Adjuvanted Zoster Subunit Vaccine

• Recombinant VZV glycoprotein E (gE) antigen and
• Liposome-based AS01b adjuvant
• Liposome is a spherical vesicle having at least one lipid bilayer

• AS01b adjuvant system contains:
  • monophosphoryl lipid A (MPL) and
  • saponin, a phytochemical (Quillaja saponaria)
Adjuvanted Zoster Subunit Vaccine Trial ZOE-50

• **Design:** Randomized, double-blind, placebo-controlled in persons ≥50 years old, stratified by age, 50-59, 60-69, 70-79, ≥ 80

• **Setting:** Multiple centers in North America, Europe, Latin America, Asia-Pacific

• **Participants:** 14,759 immunocompetent adults
  – 7344 zoster vaccine
  – 7415 placebo

Adjuvanted Zoster Subunit Vaccine Trial ZOE-50

- **Intervention:** 2 doses of subunit zoster vaccine or placebo at 2 month intervals
- **Outcomes:** Incidence of HZ and PHN

### Efficacy of Adjuvanted Zoster Subunit Vaccine ZOE-50

<table>
<thead>
<tr>
<th>Vaccine (n=7344)</th>
<th>Placebo (n=7415)</th>
<th>Vaccine Efficacy % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HZ Cases (n)</td>
<td>Incidence per 1000 person-yrs</td>
<td>HZ Cases (n)</td>
</tr>
<tr>
<td>6</td>
<td>0.3</td>
<td>210</td>
</tr>
</tbody>
</table>

97.2 (93.7-99.0)

## ZOE-50 Adverse Events and Reactogenicity

Reactogenicity Subgroup Within 7 Days After Vaccination

<table>
<thead>
<tr>
<th>Variable</th>
<th>Vaccine % (95% CI)*</th>
<th>Placebo % (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>84.4 (83.3-85.5)</td>
<td>37.8 (36.4-39.3)</td>
</tr>
<tr>
<td>-Grade 3† vaccination related</td>
<td>15.6 (14.5-16.7)</td>
<td>1.9 (1.5-2.3)</td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>81.5 (80.3-82.6)</td>
<td>11.9 (11.0-12.9)</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>Systemic reaction</td>
<td>66.1 (64.7-67.6)</td>
<td>29.5 (28.2-30.9)</td>
</tr>
<tr>
<td>-Grade 3</td>
<td>11.4 (10.5-12.4)</td>
<td>2.4 (2.0-2.9)</td>
</tr>
</tbody>
</table>

Vaccine n = 4460, Placebo n = 4466

†Grade 3 – prevented normal activity

# ZOE-50 Adverse Events and Reactogenicity

## Total Cohort Throughout Study Period

<table>
<thead>
<tr>
<th>Variable</th>
<th>Vaccine % (95% CI)*</th>
<th>Placebo % (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious adverse event</td>
<td>9.0 (8.3-9.6)</td>
<td>8.9 (8.3-9.6)</td>
</tr>
<tr>
<td>Potential immune-mediated disease</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>

*Vaccine n = 7698, Placebo n = 7713

## Efficacy of Adjuvanted Zoster Subunit Vaccine ZOE-70

<table>
<thead>
<tr>
<th>Vaccine (n=6541)</th>
<th>Placebo (n=6622)</th>
<th>Vaccine Efficacy % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HZ Cases</strong> (n)</td>
<td><strong>HZ Incidence</strong></td>
<td><strong>HZ Cases</strong> (n)</td>
</tr>
<tr>
<td>23</td>
<td>0.9</td>
<td>223</td>
</tr>
</tbody>
</table>

US Vaccination Coverage among Older Adults for Zoster Vaccine, 2015

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Coverage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zoster, ever</td>
<td>31</td>
</tr>
</tbody>
</table>

National Health Interview Survey, United States, 2015
https://www.cdc.gov/vaccines/imz-managers/coverage/adultvaxview/coverage-estimates/2015.html#table5