Zoster Vaccine for Older Adults

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Why Do We Need a Shingles Vaccine?

There are more a million new cases of shingles each year in the USA.
PAIN is a Major Manifestation of Herpes Zoster

- Prodromal Pain
- Pain during the Acute Phase
- Persisting Pain

*Postherpetic Neuralgia (PHN) - the most common debilitating complication of herpes zoster*
PHN: Clinical Features
Sensory Loss And Allodynia

Courtesy of Dr. Peter Watson, Toronto
Why Do We Need A Shingles Vaccine?

• Once shingles develops, the available treatments do not prevent PHN

Antiviral therapy
  • Modestly shortens duration of rash if initiated early
  • Even early treatment does not prevent PHN
  • We still need to choose the right antiviral drug

Corticosteroids
  • Decrease severity of acute pain
  • Do not reduce the incidence or severity of PHN
  • Side effects and toxicity argue against use

Pain medications
  • Even narcotics have limited effectiveness against chronic neuropathic pain (i.e., PHN)
  • Side effects are especially problematic in older persons
Vaccination against Shingles Presents a Unique Challenge
Vaccination against Chickenpox

• **Varicella Vaccine** is typical of vaccines against other common childhood viral diseases, such as measles, mumps and poliomyelitis. It is administered to susceptible persons prior to exogenous exposure, and it induces immunity that prevents primary infection and disease (i.e., the vaccine prevents VZV infection and Chickenpox)

• **Expectations:**
  - Vaccine Efficacy ≥95%
  - Herd Immunity
Chickenpox Vaccine Policy in the US

- **1996** – Universal one-dose childhood Chickenpox vaccination initiated in the US
  - One dose recommended at age 12-18 months, with catch-up vaccination for children up to 12 years of age

- **2006** – Policy changed to a routine two-dose program
  - 1st dose at age 12-15 months
  - 2nd dose at age 4-6 years
  - Catch-up vaccination of persons who had received one dose

- **Vaccine coverage** Reached 90% in July 2006 – June 2007 among children age 19-35 months
## Reduction in Age-Specific Chickenpox Incidence Rate

### Active Surveillance Project, 1995-2006

<table>
<thead>
<tr>
<th>Age group</th>
<th>Antelope Valley, CA (%)</th>
<th>West Philadelphia, PA (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1</td>
<td>-80</td>
<td>-94</td>
</tr>
<tr>
<td>1-4</td>
<td>-96</td>
<td>-90</td>
</tr>
<tr>
<td>5-9</td>
<td>-89</td>
<td>-94</td>
</tr>
<tr>
<td>10-14</td>
<td>-66</td>
<td>-85</td>
</tr>
<tr>
<td>15-19</td>
<td>-79</td>
<td>-90</td>
</tr>
<tr>
<td>20+</td>
<td>-86</td>
<td>-77</td>
</tr>
<tr>
<td>Total</td>
<td>-89</td>
<td>-91</td>
</tr>
</tbody>
</table>

In Contrast

When we attempt to vaccinate against herpes zoster, we are dealing with persons seen after primary infection in whom disease prevention requires changing the host-virus relationship rather than preventing primary infection. (we face a similar challenge with recurrent HSV, HIV-AIDS, and Hepatitis C)
Vaccination against Shingles

- **Zoster Vaccine** is administered to persons who are already infected with VZV. It acts by boosting the declining level of pre-existing cell mediated immunity to VZV in older adults, thereby reducing the frequency and severity of a disease (Shingles) that is caused by reactivation and multiplication of **endogenous latent VZV**

- **Expectations:**
  - Vaccine Efficacy much less than 95%
  - No Herd Immunity
Why Did We Think That A Shingles Vaccine Might Work?

1. Pathogenesis
2. Epidemiology
3. Live Attenuated Oka/Merck VZV vaccine
HSV vs. VZV
Latency and Reactivation

**HSV Simplex Virus**
- Latency: No HSV Spread within Ganglion
- Reactivation: No Neuronal Damage or Death
- Prodromal Pain: Little or No Prodromal Pain
- Postherpetic Neuralgia (PHN): No Postherpetic Neuralgia (PHN)

**Varicella-Zoster Virus**
- Latency: Extensive Spread within Ganglion
- Reactivation: Severe Neuronal Damage & Death
- Prodromal Pain: Severe Prodromal Pain
- Postherpetic Neuralgia (PHN): Postherpetic Neuralgia (PHN)
Herpes Simplex vs. Herpes Zoster
Theoretical Basis for the Shingles Prevention Study

R Edgar Hope-Simpson - 1965

In Contrast to neurons latently infected with HSV, which express no HSV proteins, neurons latently infected with VZV express Immediate Early and Early VZV proteins. Thus they may be “recognized” by host immune defenses. This may explain the critical role of Cell-Mediated Immunity in VZV latency and reactivation.
Pathogenesis of Herpes Zoster

VZV = varicella-zoster virus

HYPOTHESIS

If we can mimic the host’s immune response to herpes zoster by administering a VZV vaccine, we should be able to protect older adults from herpes zoster and PHN.
THE ZOSTER VACCINE

Dr. Michiaki Takahashi

- The Same Live Attenuated Oka/Merck Strain of VZV Used in the Varicella Vaccine Currently Licensed in the US to Prevent Chickenpox
- The Minimum Potency of the Zoster Vaccine was at least 14 Times Greater than that of Varicella Vaccine [Median = 24,600 PFU (19K-60k)]
The Shingles Prevention Study

A randomized double-blind placebo-controlled clinical trial in which 38,546 subjects ≥ 60 years of age were randomized into two age strata (60-69 and ≥70) at 22 study sites across the United States and received a single dose of live attenuated Oka/Merck VZV vaccine or placebo.

Subjects were actively followed for herpes zoster and postherpetic neuralgia (PHN) for an average of 3.13 years.
Major Challenges

- **ENROLLMENT** of a large number of subjects age 60 or older (in whom the risk of Shingles and PHN are substantial)

- **ACTIVE FOLLOW-UP** of >38,000 subjects to identify all cases of Shingles as soon as possible after rash onset; and follow each case for severity

- Develop a **QUANTITATIVE MEASURE** of SHINGLES SEVERITY

- Define a **PRIMARY ENDPOINT** that measured the impact of the vaccine on the incidence and/or severity of Shingles

- Determine **EVALUABLE CASES** of SHINGLES for Analysis of Vaccine Efficacy
How Do You Measure the Adverse Impact of Herpes Zoster on Older Persons, Since Pain is the Major Cause of their Morbidity

AND

PAIN IS SUBJECTIVE
HZ Severity of Illness Score

= AUC of Worst Pain Scores Over Time assessed with the Zoster Brief Pain Inventory (ZBPI)

The Primary End Point
(Chosen to be sensitive to an effect of Zoster Vaccine on the incidence of HZ, on the severity of HZ, or on both)

THE BURDEN OF ILLNESS (BOI) DUE TO HZ

Defined as the Sum of the HZ Severity of Illness Scores (ie, the areas under the worst pain vs. time curves) in all subjects in the Vaccine or the Placebo group.

Subjects who did not develop Shingles were assigned an HZ Severity of Illness Score = 0.
Reduction in the Incidence But Not in the Severity of HZ

Placebo

Vaccine

BOI = 250

BOI = 125
Reduction in the Severity But Not in the Incidence of HZ

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>35</td>
<td>20</td>
</tr>
<tr>
<td>75</td>
<td>20</td>
</tr>
<tr>
<td>15</td>
<td>35</td>
</tr>
<tr>
<td>15</td>
<td>40</td>
</tr>
</tbody>
</table>

BOI = 250

BOI = 125
Reduction in Both the Incidence and the Severity of HZ

Placebo

Vaccine

BOI = 250

BOI = 90
SECONDARY END POINT

THE INCIDENCE OF “CLINICALLY SIGNIFICANT” POSTHERPETIC NEURALGIA (PHN)

Where PHN is defined as HZ Pain or Discomfort with a ZBPI Worst Pain Score ≥3 for more than 90 days after HZ Rash onset
Definition of Evaluable Cases of HZ for the Analysis of Zoster Vaccine Efficacy

A Clinical Assessment by a Clinical Evaluation Committee (CEC) and a

Laboratory Assessment, primarily with a sensitive and specific PCR assay

These were separate processes, with the laboratory results having priority
The Clinical Evaluation Committee (CEC) consisted of five physicians with HZ expertise who evaluated all Suspected Cases of HZ. For each Suspected Case of HZ, each CEC member provided an independent clinical diagnosis. All cases lacking unanimity were discussed and voted upon. CEC members were blinded to treatment assignment and laboratory results.
A Vaccine to Prevent Herpes Zoster and Postherpetic Neuralgia in Older Adults

The Shingles Prevention Study

Enrolled
38,546 (41% Female)

Zoster vaccine
19,270
  Terminated before end of study
  793 (4.1%) Died
  57 (0.3%) Withdrew
  61 (0.3%) Lost to follow-up
  Completed study
  18,359 (95.3%)

Placebo
19,276
  Terminated before end of study
  792 (4.1%) Died
  75 (0.4%) Withdrew
  52 (0.2%) Lost to follow-up
  Completed study
  18,357 (95.2%)

Herpes Zoster Case Determination

Suspected Cases of HZ
1308*

315 Confirmed Cases of HZ
294 (93.3%) VZV+ by PCR
2 (0.6%) VZV+ by local virus culture
19 (6.0%) HZ by CEC only

642 Confirmed Cases of HZ
600 (93.5%) VZV+ by PCR
8 (1.2%) VZV+ by local virus culture
34 (5.3%) HZ by CEC only

*Includes two PCR-positive, unrecognized cases
CEC = Clinical Evaluation Committee

PCR Assay Results

Number of Virus-Positive Specimens

Ct value  | VZV-WT | HSV
--- | --- | ---
<10 | 12 0 | 0 0
10-14.99 | 536 | 22 13
15-19.99 | 289 | 13
20-24.99 | 79 | 13
25-31.99 | 42 | 13
32-36.35 | 13 1 |

VZV DNA copy#  | \( \approx 4.0 \times 10^8 \) | \( \approx 1.3 \times 10^7 \) | \( \approx 4.5 \times 10^6 \) | \( \approx 1.2 \times 10^4 \) | \approx 100 | 7
HSV DNA copy#  | \( \approx 1.7 \times 10^9 \) | \( \approx 5.6 \times 10^7 \) | \( \approx 1.8 \times 10^6 \) | \( \approx 6.0 \times 10^4 \) | \approx 500 | 31
<table>
<thead>
<tr>
<th>CEC Diagnosis (# of Cases)</th>
<th>PCR Result (%*)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unanimous Yes (735)</strong></td>
<td></td>
</tr>
<tr>
<td>707 with Adequate PCR specimen</td>
<td></td>
</tr>
<tr>
<td>VZV 683 (97%)</td>
<td></td>
</tr>
<tr>
<td>HSV 2 (0.3%)</td>
<td></td>
</tr>
<tr>
<td>Negative 22 (3%)</td>
<td></td>
</tr>
<tr>
<td><strong>Non-Unanimous Yes (249)</strong></td>
<td></td>
</tr>
<tr>
<td>204 with Adequate PCR specimen</td>
<td></td>
</tr>
<tr>
<td>VZV 161 (79%)</td>
<td></td>
</tr>
<tr>
<td>HSV 12 (6%)</td>
<td></td>
</tr>
<tr>
<td>Negative 31 (15%)</td>
<td></td>
</tr>
<tr>
<td><strong>Indeterminate (127)</strong></td>
<td></td>
</tr>
<tr>
<td>91 with Adequate PCR specimen</td>
<td></td>
</tr>
<tr>
<td>VZV 46 (51%)</td>
<td></td>
</tr>
<tr>
<td>HSV 11 (12%)</td>
<td></td>
</tr>
<tr>
<td>Negative 34 (37%)</td>
<td></td>
</tr>
<tr>
<td><strong>Non-Unanimous No (162)</strong></td>
<td></td>
</tr>
<tr>
<td>124 with Adequate PCR specimen</td>
<td></td>
</tr>
<tr>
<td>VZV 26 (21%)</td>
<td></td>
</tr>
<tr>
<td>HSV 20 (16%)</td>
<td></td>
</tr>
<tr>
<td>Negative 78 (63%)</td>
<td></td>
</tr>
<tr>
<td><strong>Unanimous No (33)</strong></td>
<td></td>
</tr>
<tr>
<td>28 with Adequate PCR specimen</td>
<td></td>
</tr>
<tr>
<td>VZV 0 (0%)</td>
<td></td>
</tr>
<tr>
<td>HSV 1 (4%)</td>
<td></td>
</tr>
<tr>
<td>Negative 27 (96%)</td>
<td></td>
</tr>
</tbody>
</table>

* % of cases with Adequate PCR Specimens
Vaccine Efficacy for the Herpes Zoster BOI

Efficacy (95% CI)

- 61.1% (51.1 - 69.1)
- 65.5% (51.5 - 75.5)
- 55.4% (39.9 - 66.9)

Success required a VE$_{BOI}$ point estimate of $\geq 47\%$ and a lower bound of the 95 percent confidence interval $>25\%$. 

- All Subjects Age 60–69:
  - Placebo: 5.68
  - Vaccine: 2.21
- Age 60–69:
  - Placebo: 4.33
  - Vaccine: 1.50
- $\geq$70:
  - Placebo: 7.78
  - Vaccine: 3.47

n: 19,247 19,254 10,356 10,370 8891 8884
Reduction in HZ Incidence (51%) and HZ BOI (61%)

**Placebo**
- Days 0-35: Worst Pain 35
- Days 35-75: Worst Pain 75
- Days 75+: Worst Pain 15

**Vaccine**
- Days 0-35: Worst Pain 30
- Days 35-75: Worst Pain 60
- Days 75+: Worst Pain 7

**BOI**
- Placebo: BOI = 250
- Vaccine: BOI = 97
Zoster vaccine reduced HZ Pain Interference with ADL by ~66% (Schmader et al.), providing further evidence that the HZ BOI is a valid measure of the total adverse impact of HZ on a population of older persons.
Vaccine Efficacy for the Incidence of PHN

<table>
<thead>
<tr>
<th>Efficacy (95% CI)</th>
<th>Incidence of PHN (per 1000 person years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>1.38 (47.5 - 79.2)</td>
</tr>
<tr>
<td>Vaccine</td>
<td>0.46</td>
</tr>
<tr>
<td>66.5% 65.7% 66.8%</td>
<td>0.74 (20.4 - 86.7) 0.26 (43.3 - 81.3) 0.71</td>
</tr>
<tr>
<td>All Subjects</td>
<td>19,247 n 10,356 n 8891</td>
</tr>
<tr>
<td>Age 60–69</td>
<td>19,254 n 10,370 n 8884</td>
</tr>
<tr>
<td>≥70</td>
<td></td>
</tr>
</tbody>
</table>

Success required a $\text{VE}_{\text{PHN}}$ point estimate of $\geq 62\%$ and a lower bound of the 95 percent confidence interval $>25\%$. 
Persistent Pain After Rash Healing (Postherpetic Neuralgia)

642 Placebo Recipients with Herpes Zoster

The Incidence of PHN was Reduced Even When Alternative Definitions of PHN Were Used

<table>
<thead>
<tr>
<th>PHN Defined by Cutoff Day</th>
<th>Zoster Vaccine (N=19,254)</th>
<th>Placebo (N=19,247)</th>
<th>Vaccine Efficacy $\text{VE}_{\text{PHN}}$ (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Evaluatable Cases of HZ with PHN (n)</td>
<td>Incidence of PHN (Per 1000 Person-Years)$^c$</td>
<td>Evaluatable Cases of HZ with PHN (n)</td>
</tr>
<tr>
<td>30</td>
<td>81</td>
<td>1.39</td>
<td>196</td>
</tr>
<tr>
<td>60</td>
<td>45</td>
<td>0.77</td>
<td>113</td>
</tr>
<tr>
<td>90</td>
<td>27</td>
<td>0.46</td>
<td>80</td>
</tr>
<tr>
<td>120</td>
<td>17</td>
<td>0.29</td>
<td>54</td>
</tr>
<tr>
<td>180</td>
<td>9</td>
<td>0.16</td>
<td>33</td>
</tr>
</tbody>
</table>

Success required a $\text{VE}_{\text{PHN}}$ point estimate of $\geq 62\%$ and a lower bound of the 95 percent confidence interval $>25\%$
Vaccine Efficacy for the Incidence of Herpes Zoster

Efficacy (95% CI)

- **51.3%**
  - (44.2 - 57.6)
- **63.9%**
  - (55.5 - 70.9)
- **37.6%**
  - (25.0 - 48.1)

Incidence of herpes zoster (per 1000 person years)

- **All Subjects**
  - Placebo: 11.1
  - Vaccine: 5.4
  - n: 19,247
- **Age 60–69**
  - Placebo: 10.7
  - Vaccine: 3.9
  - n: 10,356
- **≥70**
  - Placebo: 11.5
  - Vaccine: 7.2
  - n: 8891

The Shingles Prevention Study Provides a Low Estimate of HZ Severity and of the Efficacy of Zoster Vaccine

• All Study Subjects were seen as soon as possible after HZ Rash Onset and provided with State-of-the-Art treatment, including Famciclovir and pain management, without cost.
  - 86-87% of Subjects with HZ received Antiviral Treatment; 64-66% within 72 hours of rash onset
  - Average duration of opioid usage and average quantity of opioids used in Subjects with HZ were greater in the placebo group than in the vaccine group
The Shingles Prevention Study

SAFETY

The investigational zoster vaccine was well tolerated.

Deaths and percent with ≥1 SAE were the same in the vaccine and placebo groups.

Detailed Analysis shows no difference between the Zoster Vaccine and the Placebo Recipients in the number or distribution of Cardiovascular Severe Adverse Events.
The Shingles Prevention Study

SAFETY

Zoster vaccine did not cause or induce shingles

• Shingles during the 30 days post vaccination
  – Placebo group → 18 cases
  – Vaccine group → 6 cases

• Vaccine virus DNA was not detected in any of 919 PCR-confirmed cases of shingles
CRITICAL QUESTION

What Was the Influence of the Age of the Subjects on the Results?
Zoster Vaccine Efficacy

Oxman M et al. Presented at the 43rd Annual Meeting of the Infectious Diseases Society of America; October, 2005; San Francisco, CA.
Summary

• Zoster vaccine maintains its efficacy regardless of the age of the subject
  – The effect in “younger” subjects is mediated mostly by preventing HZ
  – The effect in “older” subjects is mediated mostly by attenuating HZ
Current Status

• The Shingles Prevention Study provided zoster vaccine without charge to ~14,000 placebo recipients, including 380 who had documented herpes zoster during the Study.

• A Long-Term Persistence Substudy has been initiated to assess the durability of zoster vaccine efficacy.
Zoster Vaccine: Where Do We Stand?

- On May 25, 2006, based upon the results of VA Cooperative Study #403: The Shingles Prevention Study, the FDA licensed zoster vaccine (ZOSTAVAX™, Merck) for the prevention of herpes zoster in immunocompetent adults aged ≥60 years.

- On October 25, 2006, the ACIP made a provisional policy recommendation to administer a single dose of zoster vaccine to adults aged ≥60 years for the prevention of herpes zoster and postherpetic neuralgia — whether or not they report a prior episode of herpes zoster (MMWR June 6, 2008).

- This recommendation has now been incorporated into the CDC’s Adult Immunization Schedule.
# Adult Vaccine Schedule

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Specifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetanus, diphtheria, pertussis (Td/Tdap)</td>
<td>1 dose Td booster every 10 years (substitute Tdap for Td if 60-64 years old)</td>
</tr>
<tr>
<td><strong>Zoster</strong></td>
<td>1 dose ≥60 years of age</td>
</tr>
<tr>
<td>Influenza</td>
<td>1 dose annually</td>
</tr>
<tr>
<td>Pneumococcal polysaccharide</td>
<td>1 dose ≥65 years of age</td>
</tr>
</tbody>
</table>

Recommended for all persons in this category who meet the age requirements and who lack evidence of immunity (e.g., lack of documentation of vaccination or no evidence of prior infection).


### Results of Vaccinating All Persons ≥60 Years of Age

<table>
<thead>
<tr>
<th></th>
<th>Herpes Zoster</th>
<th>PHN (&gt;90 d)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cases per year</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>without vaccine</strong></td>
<td>556,200</td>
<td>69,600</td>
</tr>
<tr>
<td><strong>Cases eliminated</strong></td>
<td>283,700</td>
<td>46,400</td>
</tr>
<tr>
<td><strong>by vaccination</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Remaining cases</strong></td>
<td>272,500</td>
<td>23,200</td>
</tr>
</tbody>
</table>

Immunology Substudy
Baseline by Age

VZV-CMI declines with increasing age
Begins in early adulthood and continues with increasing age

VZV antibody does not decline with age

Levin, M., et al. JID 2008:197 825-835
At 6 weeks after vaccination, immune responses in vaccine recipients measured by all three assays were significantly increased, compared with placebo.

The magnitude of the VZV CMI response to the vaccine was greater in subjects 60 - 69 years of age than in those ≥70, but little difference in antibody response.

Levin, M., et al. JID 2008: 197: 825-835
• Higher levels of cell-mediated immunity to VZV correlate with reduced severity of disease and with a lower incidence of PHN

• Higher levels of antibody to VZV do not
RCF at First Visit vs. HZ Severity of Illness and Development of PHN

CMI Substudy: Increased Antibody to VZV Correlated with Increased Herpes Zoster Severity of Illness and PHN

CMI CMI Substudy: Substudy:

Increased Antibody to VZV Correlated with Increased Herpes Zoster Severity of Illness and PHN.
Unanswered Questions

• the rationale for the ACIP recommendation to administer zoster vaccine to persons with a history of HZ
• the risk that recipients of zoster vaccine will transmit vaccine virus to susceptible contacts
• safety and efficacy in persons ≥80 years of age
• the potential use of zoster vaccine in persons <60 years of age
• the duration of zoster vaccine efficacy (¿ booster dose)
• the simultaneous administration of zoster vaccine and other vaccines recommended for adults, such as influenza vaccine
• the potential use of zoster vaccine in immunocompromised persons
• The impact of childhood Varicella Vaccination on the incidence and severity of Herpes Zoster in adults
• the Cold Chain and Medicare Part D
Antibody Response to ZOSTAVAX™ plus INFLUENZA VACCINE (Kerzner et al. JAGS 55:1499, 2007)
## Antibody Response to Zostavax + Pneumovax
(MacIntyre CR, et al. Poater presented at the 2008 ICAAC-IDSA Meeting)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Concomitant Group (N=235)</th>
<th>Non-Concomitant Group (N=236)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Response</td>
</tr>
<tr>
<td>GMT Week 4</td>
<td>217</td>
<td>371.6</td>
</tr>
<tr>
<td>GMFR</td>
<td>217</td>
<td>1.9</td>
</tr>
</tbody>
</table>

### PnPs Serotype 3

| GMT Week 4 | 219   | 1.1    | (1.0, 1.2)  | 228   | 1.2    | (1.1, 1.4)  |
| GMFR        | 219   | 2.1    | (1.9, 2.4)  | 227   | 2.3    | (2.1, 2.5)  |

### PnPs Serotype 14

| GMT Week 4 | 219   | 25.7   | (21.8, 30.3)| 228   | 26.5   | (22.9, 30.8)|
| GMFR        | 219   | 3.9    | (3.4, 4.5)  | 227   | 4.3    | (3.7, 5.0)  |

### PnPs Serotype 19A

| GMT Week 4 | 219   | 10.5   | (8.7, 12.7)| 228   | 10.5   | (8.7, 12.6)|
| GMFR        | 219   | 5.3    | (4.6, 6.1)  | 227   | 5.1    | (4.4, 6.0)  |

### PnPs Serotype 22F

| GMT Week 4 | 219   | 2.5    | (2.1, 3.0)  | 228   | 2.8    | (2.3, 3.3)  |
| GMFR        | 219   | 7.5    | (6.3, 8.8)  | 227   | 9.6    | (8.2, 11.2) |
The Concept of Relative vs. Absolute Benefit
Vaccine Efficacy for the Herpes Zoster BOI

Efficacy (95% CI)  
- **Placebo**: 55.4% (39.9 - 66.9)
- **Vaccine**: 65.5% (51.5 - 75.5)

Success required a VE_{BOI} point estimate of ≥ 47% and a lower bound of the 95 percent confidence interval >25.

- **All Subjects Age 60–69**: 61.1% (51.1 - 69.1)  
  - Placebo: 5.68, Vaccine: 2.21
  - **A reduction of 29,325**
- **≥70**: 55.4% (39.9 - 66.9)  
  - Placebo: 7.78, Vaccine: 3.47
  - **A reduction of 38,445**
Relative vs. Absolute Benefit

• Frequency and Severity of HZ and PHN increase with increasing age

• Thus even if vaccine efficacy is reduced in persons ≥80 years of age, the absolute benefit may be as great or greater than in persons 60-69 years of age

• For example, a 40% reduction in a HZ Severity of Illness Score of 800 (\(=320\)) is greater than a 60% reduction in a HZ Severity of Illness Score of 400 (\(=240\))