Herpes zoster vaccination and quality of life in ageing population

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Conflict of Interest, 2017

• Honoraria for lecturing or as member of advisory boards from Pfizer, GSK und Sanofi-Pasteur

• Honoraria for conducting clinical vaccine trials for GSK and Pfizer
Zoster ophthalmicus
Several studies have shown that the incidence of HZ increases substantially with age\textsuperscript{1,2}

France: Incidence

The incidence of HZ between 2007 and 2010¹

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>0–9</th>
<th>10–19</th>
<th>20–29</th>
<th>30–39</th>
<th>40–49</th>
<th>50–59</th>
<th>60–69</th>
<th>70–79</th>
<th>80–89</th>
<th>≥90</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007</td>
<td>2</td>
<td>2</td>
<td>2</td>
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<tr>
<td>2008</td>
<td>2</td>
<td>2</td>
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<td>2</td>
<td>2</td>
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<td>2</td>
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<tr>
<td>2009</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
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<td>2</td>
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<tr>
<td>2010</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
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</tbody>
</table>

HZ incidence has remained stable between 2007 and 2010 at 3.82 cases per 1,000 person-years, but HZ and PHN incidences increase with age

The percentage of patients with HZ who experienced PHN* 3 months after initial diagnosis²

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>50–60</th>
<th>60–70</th>
<th>70–80</th>
<th>≥80</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of HZ cases with persisting pain</td>
<td>20</td>
<td>25</td>
<td>30</td>
<td>35</td>
</tr>
</tbody>
</table>

² PHN defined as persistent pain occurring at least 1 month after initial diagnosis of HZ
Increase in Herpes zoster in high income countries

• May be related to an increase in varicella vaccination?
• However, incidence of HZ was increasing prior to varicella vaccination programs

• Reduced exposure to varicella zoster virus
• More immune-compromised patients
• Demographic and societal changes
  – decreasing % of women with >1 child/no of children per women
  – More single-parent families
  – decreasing contact between grandparents and grandchildren
HZ is caused by the reactivation of varicella zoster virus

Dorsal root ganglion

Degeneration of neurons

VZV virions in neurons

Esiri and Tomlinson J Neurol Sciences 1971

Scarring

Surviving nerve cells
Latent VZV infection and reactivation

- VZV primary infection induces VZV T-cell immune memory
- VZV immunity may be boosted periodically by exposure to varicella or silent reactivation from latency
- VZV-specific memory T-cells decline with age or in specific immune impairment conditions

The decline below a threshold correlates with an increased risk of HZ disease

Immunity to HZ correlates with VZV T-cell levels

HZ: herpes zoster; VZV: varicella zoster virus
Licenced zoster vaccines

Live-attenuated zoster vaccine (ZVL)
- Indicated for prevention of herpes zoster in individuals 50 years of age and older.
- First licensed 2006 (60 y) resp. 2011 (50 y)
- 1 dose

HZ/su (adjuvanted subunit vaccine)
- Antigen: recombinant VZV Glycoprotein E (gE) + Adjuvant System AS01B
- Indicated for prevention of herpes zoster in adults aged 50 years and older.
- 2 Doses (month 0, 2)
- First licensed 10/2017 (Canada, USA)
Current zoster vaccine recommendations

**USA, 2007-2015**

Vaccination coverage

**General recommendations**

- UK: 70-79 y
- Canada: 60+ years
- France: 65-74 years
- Austria: 50 + years
- Saxonia (Germany): 50+
- Germany: not generally recommended

- [https://www.has-sante.fr/portail/upload/docs/application/pdf/2015-06/zostavax_en_sapub_ct13478_val.pdf](https://www.has-sante.fr/portail/upload/docs/application/pdf/2015-06/zostavax_en_sapub_ct13478_val.pdf)
- [https://www.bmgf.gv.at/home/Impfplan](https://www.bmgf.gv.at/home/Impfplan)
- [https://www.slaek.de/media/dokumente/02medien/Patienten/gesundheitsinformationen/impfen/Synopsis_2017_.pdf](https://www.slaek.de/media/dokumente/02medien/Patienten/gesundheitsinformationen/impfen/Synopsis_2017_.pdf)
HZ/su pivotal phase III programme: ZOE-50 and ZOE-70\textsuperscript{1,2}

*New England Journal of Medicine, 2015, 2016*

<table>
<thead>
<tr>
<th>Study design and objectives</th>
<th>ZOE-50\textsuperscript{1} (Zoster-006)</th>
<th>ZOE-70\textsuperscript{2} (Zoster-022)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>Randomised, observer-blind, placebo-controlled, multicentre, multinational (North America, Europe, Latin America, Asia-Pacific)</td>
<td></td>
</tr>
<tr>
<td>Schedule</td>
<td>2 doses administered 2 months apart</td>
<td></td>
</tr>
<tr>
<td>Primary objectives</td>
<td>$\text{VE}_{HZ}$ in subjects $\geq 50$ years of age</td>
<td>$\text{VE}_{HZ}$ in subjects $\geq 70$ years of age</td>
</tr>
<tr>
<td>Primary objectives (pooled analysis)</td>
<td>$\text{VE}_{PHN}$ in individuals $\geq 70$ years of age</td>
<td>$\text{VE}_{HZ}$ efficacy in individuals $\geq 70$ years of age</td>
</tr>
<tr>
<td>Actual enrollment</td>
<td>16160</td>
<td>14816</td>
</tr>
</tbody>
</table>

**ZOE-50 and ZOE-70 studies conducted at the same sites**

Subjects $\geq 70$ years of age were randomly assigned to ZOE-50 or ZOE-70

PHN, postherpetic neuralgia; VE, vaccine efficacy

Efficacy of an Adjuvanted Herpes Zoster Subunit Vaccine in Older Adults

Himal Lal, M.D., Anthony L. Cunningham, M.B., B.S., M.D., Olivier Godeaux, M.D.,

ZOSTER-006 (Final Analysis): Vaccine efficacy against first or only episode of HZ during the entire study period in adults ≥50 YOA, overall and by age strata (mTVC)

<table>
<thead>
<tr>
<th>Age strata</th>
<th>HZ/su</th>
<th>Placebo</th>
<th>Vaccine Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>n</td>
<td>T(year)</td>
</tr>
<tr>
<td>≥50 YOA **</td>
<td>7344</td>
<td>6</td>
<td>23297.0</td>
</tr>
<tr>
<td>50-59 YOA *</td>
<td>3492</td>
<td>3</td>
<td>11161.3</td>
</tr>
<tr>
<td>60-69 YOA *</td>
<td>2141</td>
<td>2</td>
<td>7007.9</td>
</tr>
<tr>
<td>≥70 YOA **</td>
<td>1711</td>
<td>1</td>
<td>5127.9</td>
</tr>
</tbody>
</table>

N = number of subjects included in each group
n = number of subjects having at least one confirmed HZ episode

HZ/su greatly reduced HZ complications, such as PHN, among all groups ≥50 years of age*1,2

<table>
<thead>
<tr>
<th>Age, years</th>
<th>HZ/su</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PHN cases (n)</td>
<td>Rate (cases per 1000 person-years)</td>
</tr>
<tr>
<td>≥50</td>
<td>4 (13881)</td>
<td>0.1</td>
</tr>
<tr>
<td>≥70</td>
<td>4 (8250)</td>
<td>0.1</td>
</tr>
</tbody>
</table>

- In a post-hoc pooled analysis from ZOE-50 and ZOE-70, HZ/su also reduced non-PHN complications (HZ vasculitis, stroke, disseminated, ophthalmic, neurological and visceral disease)2
  - VE in subjects ≥50 years of age: 93.7% (95% CI 59.5, 99.9)
  - VE in subjects ≥70 years of age: 91.6% (95% CI 43.4, 99.8)

PHN defined as HZ-associated pain rated as ≥3 on a 0–10 scale, occurring or persisting for at least 90 days following the onset of rash using Zoster Brief Pain Inventory questionnaire. Pooled data from ZOE-50 (subjects ≥50 years of age) and ZOE-70 (subjects ≥70 years of age)

*All subjects randomised in the study who received a second dose of the vaccine. Final analysis data cut-off date: July 1, 2014; mean follow-up 3.8 years; †p<0.001 for both comparisons

CI, confidence interval; HZ/su, herpes zoster subunit vaccine; PHN, postherpetic neuralgia; VE, vaccine efficacy

Vaccine efficacy against HZ for ZVL and HZ/su following vaccination

Note: The Shingles Prevention Study, Short-term Persistence Study, and Long-term Persistence Study followed the same study population in a randomized control trial over time.


Not based on head to head data; Shingrix™ and Zostavax™ have not been tested head to head. Shingrix data based on ph III clinical trials.
Immune response across age segments

HZ/su vaccine

ZVL vaccine

Not based on head to head data; Shingrix™ and Zostavax™ have not been tested head to head. Shingrix data based on ph III clinical trials.
9 years follow-up of immune response of HZ/su vaccine

Predictor of duration of efficacy

Median frequencies of gE-specific CD4⁺ T-cells expressing ≥2 activation markers (ATP cohort for immunogenicity)

Pauksens K et al. 42nd Annual International Herpesvirus Workshop, Ghent, Belgium, July 29 – August 2, 2017
# Brief Overview of Zoster-048

*Prospective, group-matched, non-randomized trial*

<table>
<thead>
<tr>
<th></th>
<th>Previous ZVL</th>
<th>No Previous ZVL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Experimental design</strong></td>
<td>Phase III, prospective, group-matched, non-randomized, open label, multicenter study in US</td>
<td></td>
</tr>
<tr>
<td><strong>HZ vaccination history</strong></td>
<td>ZVL ≥5 years prior</td>
<td>No previous HZ vaccine</td>
</tr>
<tr>
<td><strong>Age range</strong></td>
<td>≥65 years of age</td>
<td></td>
</tr>
</tbody>
</table>
| **Co-primary objectives**       | • Compare anti-gE antibody concentrations 1 month post-dose 2 (non-inferiority)*  
                                 | • Safety and reactogenicity up to 1 month post dose 2                        |                                          |
| **Secondary objectives**        | • Humoral immune response and cell-mediated immunity at baseline, 1 month post-dose 1, and 1 and 12 months post-dose 2  
                                 | • Safety up to 12 months post-dose 2 (ongoing)                               |                                          |

*Non-inferiority: upper limit of two-sided 95% CI of adjusted geometric mean concentration ratio (No Previous ZVL over Previous ZVL 1 month post-dose 2) is below 1.5 for anti-gE antibodies.*
Month 3 Cellular Immune Responses Similar Between Groups and Consistent With ZOE-50 Trial

gE-specific CD4⁺[2+] frequencies

Zoster-048
(mean: 70.9 years of age)

Pre-vaccination (M0) | Post-dose 1 (M1) | Post-dose 2 (M3)
67 | 425 | 2312
58 | 427 | 2214

ZOE-50
(mean: 64.1 years of age)

Pre-vaccination (M0) | Post-dose 2 (M3)
90 | 1644

Previous ZVL, received live-attenuated zoster vaccine (Zostavax®) ≥5 years earlier; No Previous ZVL, never received live-attenuated zoster vaccine (Zostavax®). CD4⁺[2+], CD4+ T-cells secreting at least two activation markers (IFN-γ, IL-2, TNF-α, CD40L); gE, glycoprotein E; M, month; Q1, Quartile 1=25th percentile; Q3, Quartile 3=75th percentile; ZOE-50, zoster efficacy trial ≥50 years of age.
October 25, 2017

ACIP: New Vaccine Recommendations for Shingles Prevention

The Centers for Disease Control and Prevention (CDC)'s Advisory Committee on Immunization Practices (ACIP) voted in favor for the use of Shingrix (zoster vaccine recombinant, adjuvanted; GlaxoSmithKline) for the prevention of shingles (herpes zoster).

The ACIP recommends Shingrix for the prevention of herpes zoster and related complications for immunocompetent adults aged ≥50 years and adults who previously received Zostavax (zoster vaccine live; Merck). The Committee voted that Shingrix is preferred over Zostavax for the prevention of zoster and related complications.
Co-administration

Immunogenicity and safety of an adjuvanted herpes zoster subunit vaccine co-administered with seasonal influenza vaccine in adults aged 50 years and older

Tino F Schwarz, Naresh Aggarwal, Beate Moeckesch, Isabelle Schenkenberger, Carine Claeys, Martine Douha, Olivier Godeaux, Katrijn Grupping, Thomas C Heineman, Marta Lopez Fauqued

The Journal of Infectious Diseases, jix481, https://doi.org/10.1093/infdis/jix481

Published: 26 September 2017

Conclusions

No interference in the immune responses to either vaccine was observed when co-administered and no safety concerns were identified.
Conclusion

• HZ/su vaccine is a milestone in the prevention of an infectious disease in an ageing population
• HZ/su vaccine will substantially reduce the burden of disease (HZ and PZN)
• Improve the quality of life in the elderly
• Will reduce costs for the health care system
• Current national zoster vaccine recommendations will have to be adopted