Herpes zoster: review of evidence

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on behalf of the
SAGE Working Group on varicella and herpes zoster

SAGE meeting
WHO, Geneva, Switzerland
April 2nd, 2014
Context

• SAGE VZV Working Group tasked to review evidence to formulate recommendations on the use of herpes zoster vaccines
  - Update the 1998 varicella vaccine position paper

• Evidence included:
  - Epidemiology & global disease burden
  - Vaccine safety & efficacy
  - Effectiveness & cost-effectiveness

Objective

• Present the available evidence related to herpes zoster
Herpes zoster

Definition

- Herpes Zoster: reactivation of varicella zoster virus (VZV), leading to blisters in a dermatomal distribution
  - Following initial infection (varicella), VZV establishes permanent latent infection in dorsal root ganglia
  - Years to decades later VZV reactivates
  - VZV virions reappear & spread to skin through peripheral nerves

* Slide from R Harpaz CDC
Prodromal pain
Manifestations & Symptoms

- ~74% herpes zoster patients have pain prior to rash onset
- Mean pain severity: 6/10
- Median duration: 4 days
- % overall herpes zoster burden of illness: 9%
- Starts as abnormal skin sensation, itching or tingling
  - Precedes rash by about 4 days
  - Results in medical consultations

Ref: Drolet Human Vaccines 2013, Benbernou European Journal of Pain 2011 Mean pain severity (ZBPI worst pain score) estimated among individuals reporting clinically significant pain (i.e., worst ZBPI score ≥ 3) during each phase of the disease
Herpes zoster
Manifestations & Symptoms

- 30% lifetime risk
- 95% of patients have pain at rash onset
- Mean pain severity at rash onset: 6/10
- Median duration of herpes zoster episode: 33 days
- % overall herpes zoster burden of illness:
  - Acute/subacute: 70%

Ref: Drolet Human Vaccine 2013
Herpes zoster
Manifestations & Symptoms

• Rash:
  - Dermatomal distribution: 1) thoracic > 2) lumbar, trigeminal, & cervical > 3) sacral, other cranial dermatomes

• Key symptom: Pain
  - Can be excruciating
  - Described as aching, burning, stabbing, shock-like
  - Often associated with:
    • Altered or painful sensitivity to touch
    • Provoked by trivial stimuli like bed sheets or breeze
    • Exaggerated, prolonged response to pain
    • Unbearable itching

* Slide adapted from R Harpaz CDC
Herpes zoster
Impact on quality of life (patients 50+ years old)

Ref: Drolet Human Vaccines 2013
Post-herpetic neuralgia (PHN)
Definition, Manifestations & Symptoms

- PHN: Pain persisting more than 90 days after rash onset
  - Definition may vary, linked to long-lasting pain
- 22% (8-26%) of herpes zoster patients develop PHN
  - Proportion very dependent on definition
- Mean severity at PHN onset: 6/10
- Median duration from rash onset: 170 days
- % overall herpes zoster burden of illness: 20%

Ref: Drolet Human Vaccines 2013; Drolet J Pain 2010; Drolet Human Vaccines 2013; Opstelten Pain 2007; Oxman NEJM 2005
Post-herpetic neuralgia (PHN)

Definition, Manifestations & Symptoms

- Pain persists months and even years (median=6 months)
- PHN prevention with antivirals (<72 hrs after rash onset):
  - reduces acute pain
  - hastens rash resolution
  - ability to prevent PHN remains controversial
- PHN treatment:
  - Tricyclic antidepressants, anticonvulsants, topical agents, opioids, nerve blocks, others
  - Partial or inconsistent efficacy
  - Important side effects

* Slide adapted from R Harpaz CDC, Ref: Drolet Human Vaccines 2013
Post-herpetic neuralgia
Impact on quality of life (patients 50+ years old)

Ref: Drolet, *Human Vaccines* 2013; Schmader CID 2001: **Physical** (Chronic fatigue, Weight loss, Inactivity, Insomnia), **Social** (change in social life), **Psychological** (Anxiety, Depression, Suicidal ideation), **Functional** (Interferes with dressing, eating, bathing, cooking)
Other Herpes zoster complications

Manifestations & Symptoms

• Herpes zoster Ophthalmicus (HZO):
  - Ophthalmic division of trigeminal nerve
  - ~15% of cases
  - If untreated, 50-70% develop acute ocular complications
    • chronic complications, reduced vision, even blindness

• Neurologic:
  - Invasion by VZV of vascular or neurologic structures
  - Encephalitis, myelitis, optic neuritis, palsies, stroke syndromes
  - Hearing impairment, vertigo, loss of taste sensation

• Deaths mostly occur among the immunocompromised
  - 0.25-0.51 per 1 million population\[1\]
  - 7-25 per 100,000 case\[1,2\]

Epidemiology & Burden of Disease
Global Burden of Herpes zoster

Data availability

- Incidence of Herpes zoster and mortality data
  - Most data from Europe, North America and Australia
  - No data from low and low-middle income countries (LMIC)[1]

Herpes zoster incidence by age
Highly consistent findings between high income countries
Lifetime risk=20-35%, Steep increase in incidence with age
Main concern about varicella vaccination

Unknown impact on the epidemiology of zoster

• Herpes zoster may occur more frequently in adults who have not been boosted by varicella contacts
  - Individuals with > 3 exposures to varicella have $1/5^{th}$ risk of zoster compared to unexposed \[1\]
  - Adults living with children have higher exposure to varicella and significantly lower herpes zoster incidence \[2\]

• If this is so then reduction of varicella incidence after mass vaccination could increase zoster incidence

• Note: Evidence of the impact of exposure to varicella on risk of zoster is still inconclusive \[3\]

Predicted impact of varicella vaccination on Herpes zoster

Mathematical models from Canada, Finland, England and Wales, and Belgium predict very similar dynamics after varicella vaccination.

Ref: Van Hoek Vaccine, 2012; Brisson model; Blicke Human Vaccines & Immunotherapeutics 2013; Karhunen Epidemiol Infect, 2010
Increase in Herpes zoster
Prior to varicella vaccination in high income countries

Canada

United Kingdom

Year

Rate (per 100,000 year)

Ref: Brisson Epidemiol Infect 2001
Herpes zoster after varicella vaccination

Increase in herpes zoster in most high income countries

Example from Québec

<table>
<thead>
<tr>
<th>Year</th>
<th>Private Consult. rate per 10,000 pers-yr</th>
<th>Public Consult. rate per 10,000 pers-yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1992</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>1994</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>1996</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>1998</td>
<td>40</td>
<td>40</td>
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<tr>
<td>2000</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>2002</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>2004</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>2006</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>2008</td>
<td>90</td>
<td>90</td>
</tr>
</tbody>
</table>

&. Private=23%, Public= 52% (2006), 89% (2007) and 90% (2008);
Herpes zoster after varicella vaccination

Increase in herpes zoster in most high income countries

Example from Canada and US

**Fig. 1.** Crude rates of medically attended shingles per 1000 population (with 95% confidence intervals and LOESS fit curve), 1994–2010.

**Figure.** HZ incidence among Medicare beneficiaries older than 65 years, by age group, 1992–2010.

REF. Russell Vaccine 2013; Hales Ann Int Med 2013
Increase in Herpes zoster
Evidence from high income countries (HIC)

- Herpes zoster is increasing in HIC
  - cannot directly attribute the increase to varicella vaccination
  - herpes zoster was increasing prior to vaccination programs

- Why is herpes zoster increasing?
  - reduced exposure to VZV?
    • varicella vaccination
    • demographic/societal changes in HIC
  - more immunocompromised?

- Too early to determine whether increase in herpes zoster is partially due to varicella vaccination

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&. decreasing % women with ≥ 1 child and numbers of children per woman, increasing # single-parent families and decreasing contact between grandparents and grandchildren
Herpes zoster severity increases with age

Hospitalizations and Length of Stay

Ref: Brisson *Epidemiol Infect* 2001
Herpes zoster
Risk factors

- **Immunosuppression from any cause**
  - hematologic malignancies, HIV and immunosuppressive medications
  - relative risk (RR) vs. non-immunosuppressed > 10-fold\(^1\-^2\)

- **Race**
  - Blacks (vs whites) RR=0.35-0.46\(^3\-^4\)
  - People born in countries with late varicella onset RR=0.56\(^4\)

- **Sex**
  - Women (vs men) RR=1.1, placebo arm zoster vaccine trial\(^5\)
  - Results not consistent between studies\(^4\)

- **Exposure to children**
  - Studies suggest protective effect of exposure to children \(^4,^6,^7\)
  - Results are not consistent between studies\(^4,^8\)

- **Stress or trauma, diabetes and higher social class\(^9,^10\)**
Post-herpetic neuralgia

Duration of pain

Post-herpetic neuralgia
Incidence by age, UK

Ref: Edmunds Vaccine 2001
## Post-herpetic neuralgia

### Risk factors

<table>
<thead>
<tr>
<th>Age</th>
<th>Income</th>
<th>Functional problems</th>
<th>Pain at recruitment</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-60</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>61-70</td>
<td>≤$20,000</td>
<td>$20-39,999</td>
<td>No</td>
</tr>
<tr>
<td>≥70</td>
<td>≥$40,000</td>
<td>≥$50,000</td>
<td>Yes</td>
</tr>
<tr>
<td>Ref</td>
<td>Ref</td>
<td>Yes</td>
<td>Ref</td>
</tr>
<tr>
<td>No Mild (0-2)</td>
<td>Moderate (3-6)</td>
<td>Severe (≥7)</td>
<td></td>
</tr>
</tbody>
</table>

Ref: Drolet *Journal of Pain* 2010
Vaccine efficacy, duration & safety
Herpes zoster vaccine characteristics

• Currently available - Merck live Oka/Merck VZV vaccine

• Licensed in over 60 countries

• Indicated in immunocompetent individuals aged ≥ 50 years

• Live vaccine - contraindicated in immunosuppressed

• Potency 18,700-60,000 PFU per dose
  - Median potency 24,600 PFU
  - 14 x as potent as varicella vaccine
Clinical studies

- Shingles Prevention Study (SPS)$^{[1]}$
  - Randomized clinical trial
  - 38,546 individuals aged $\geq 60$ years

- Randomized trial among younger subjects$^{[2]}$
  - 22,439 individuals aged 50-59 years

- Short-term Persistence Study$^{[3]}$
  - Continuation of follow-up of 14,000 SPS subjects

Efficacy of herpes zoster vaccine (VE)
Clinical trials (short term) [1,2]

<table>
<thead>
<tr>
<th>Age</th>
<th>Incidence of HZ</th>
<th>Burden of illness</th>
<th>Incidence of PHN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>V</td>
<td>P</td>
<td>VE (95% CI)</td>
</tr>
<tr>
<td>50-59 yrs</td>
<td>2.0</td>
<td>6.6</td>
<td>70 (54-81)</td>
</tr>
<tr>
<td>60-69 yrs</td>
<td>3.9</td>
<td>10.8</td>
<td>64 (56-71)</td>
</tr>
<tr>
<td>≥ 70 yrs</td>
<td>7.2</td>
<td>11.5</td>
<td>38 (28-52)</td>
</tr>
</tbody>
</table>

V: Vaccine group; P: Placebo group; VE: Vaccine efficacy
Burden of illness score is a composite measure of HZ incidence, severity and duration of pain

Vaccine effectiveness US post-licensure studies (≥60 years):

• Herpes zoster = 55%[3] and 48%[4]
• Ophthalmic herpes zoster = 63%[3]
• Hospitalizations coded as herpes zoster = 65%[3]
• PHN = 59%[4]
• Immunosuppressed = 37% (95%CI: 6-58)[4]

Duration of herpes zoster vaccine efficacy (VE) Shingles Prevention Study (SPS), Short-Term Persistence Substudy (STPS), and the Combined SPS and STPS

<table>
<thead>
<tr>
<th>Time since randomization</th>
<th>Incidence of HZ VE, % (95% CI)</th>
<th>Burden of illness VE, % (95% CI)</th>
<th>Incidence of PHN VE, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years 0.0-4.9</td>
<td>51 (44-58)</td>
<td>61 (51-69)</td>
<td>67 (48-79)</td>
</tr>
<tr>
<td>Years 3.3-7.8</td>
<td>40 (18-56)</td>
<td>50 (14-71)</td>
<td>60 (-10-87)</td>
</tr>
<tr>
<td>Years 0.0-7.8</td>
<td>49 (52-55)</td>
<td>59 (49-67)</td>
<td>65 (47-77)</td>
</tr>
</tbody>
</table>

Ref: Schmader CID 2012
Safety of herpes zoster vaccine

Immunocompetent adults ≥ 50 years

• The vaccine was well-tolerated in the SPS[1,2]
  - Similar proportions (1.4%) of participants who received the vaccine (n=19,270) or the placebo (n=19,276) reported serious adverse events
  - Varicella-like rash at the site of injection was the only adverse event statistically more frequent among vaccinated

• Safety of the vaccine was confirmed in the RCT among younger subjects (50-59 years) [3]
  - 0.6% and 0.5% of participants who received the vaccine (n=11,211) or the placebo (n=11,228) reported serious adverse events

• Vaccine safety has been demonstrated in post-licensure studies[4-7]

Concomitant administration of Herpes zoster vaccines with other vaccines

- Concomitant administration of inactivated influenza and herpes zoster vaccines:
  - No reduction in immunogenicity\(^1\)

- Concomitant administration of pneumococcal polysaccharide and herpes zoster vaccine:
  - No significant difference in adverse events between arms concomitantly or non-concomitantly vaccinated\(^2\)
  - Herpes zoster vaccine efficacy not affected\(^3\)

Safety of herpes zoster vaccine
Immunocompromised adults

• Herpes zoster vaccine is contra-indicated in persons who are immunosuppressed from any cause

• Safety in immunocompromised persons has been examined in post-licensure studies[1-5]:
  - Authors claim no significant increased risk in serious adverse effects in these studies
  - However, studies are limited, particularly in terms of sample size

Cost-effectiveness
Literature review

Cost-effectiveness of herpes zoster vaccination

• Review from Szucs & Pfeil\textsuperscript{[1]}, including new publications\textsuperscript{[2]}

• 12 studies:
  - All from Europe and North America
  - 5 out of 12 funded by industry

• Consistent Results:
  - All studies except one considered vaccination to be cost-effective
    • Van Lier (2010) because of low CEA threshold (€20,000) in Netherlands
  - Herpes zoster vaccination is cost-effective when:
    • the vaccine is given at about 65-70 years of age, and
    • vaccine protection against PHN is longer than 10-15 years\textsuperscript{[2]}

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Cost-effectiveness of herpes zoster vaccination

Quality of the evidence

- **Study quality** - Generally good
  - ‘moderate’ to ‘moderate to good’ according to the BMJ criteria[1]

- **Consistency of findings** - Cost-effective
  - if vaccine is given at about 65-70 years of age
    - dependent on duration of protection
  - if vaccine protection against PHN is longer than 10-15 years

- **Magnitude of effect** - Variable
  - Studies vary from very cost-effective to not cost-effective

- **Evidence** - Indirect
  - All are modeling studies

**Ref:** 1. Szucs Pharmacoeconomics 2013
Key remaining issues

- Duration of protection of the zoster vaccine?
  - Recent trial results indicate possible waning of protection\[^{[1]}\]
  - Key issue is long-term protection against severe zoster and PHN, which is unclear\[^{[1]}\]
    - Burden of Illness (BOI): $\text{VE}_{0-5\text{yrs}}=61\% \ (51 \text{ to } 69) \ vs \ \text{VE}_{3-8\text{yrs}}=50\% \ (14 \text{ to } 71)\]
    - PHN: $\text{VE}_{0-5\text{yrs}}=67\% \ (48 \text{ to } 79) \ vs \ \text{VE}_{3-8\text{yrs}}=60\% \ (-10 \text{ to } 87)\]

- Increase in herpes zoster after varicella vaccination?
  - Could have an impact on age at vaccination
  - May be cost-effective to vaccinate at younger age

- Epidemiology and burden of disease of herpes zoster in low to middle income countries?

Thanks!