Zoster vaccine

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Disclaimer

I have received no remuneration for giving this or any other talk about zoster vaccine.

Some slides on shingles epidemiology have been adapted from information supplied by bioCSL, makers of Zoster vaccine.
Shingles

- Background
- Epidemiology
- Complications inc Postherpetic Neuralgia (PHN)

Current vaccine:

Live zoster vaccine

- Clinical data
  - Efficacy / safety in adults aged 60+
  - Efficacy and safety in adults aged 50-59 years

Future vaccine:

“Dead”: Adjuvanted Herpes Zoster Subunit Vaccine
Varicella Zoster Virus

Chickenpox (Varicella)
1° infection

Shingles (Zoster)
Latent virus reactivates later in life
Varicella Zoster Virus

Chickenpox (Varicella)

1º infection

- Typically Childhood
- Highly contagious
- **Inhalation** of infective respiratory droplets or **direct contact** with VZV
Varicella Zoster Virus

Chickenpox (Varicella)

1° infection

Symptoms:
- Fever
- Rash – itchy, crops of maculopapular/vesicular lesions
- ~ 5% subclinical

Generally mild
- Complications can include bacterial infection, pneumonia, CNS

Universal varicella vaccine - included on Australia National Immunisation Program in 2005
Varicella Zoster Virus

Viral latency established after chickenpox
Varicella Zoster Virus

Shingles (Zoster)
Latent virus reactivates later in life
Zoster

painful, unilateral, dermatomal rash

Reactivation triggers - poorly understood

Diminished cell-mediated immunity (CMI)
- ie mediated by sensitised T lymphocytes, not antibodies

CMI diminishes with:

**Increasing age**

**Immunocompromise**
- Malignancy, HIV infection
- Immunosuppressants e.g. organ transplant, autoimmune diseases
Risk increases with age

Incidence will increase further as population ages
Complications - also increase with age

Occur in 13-26% of patients

Older adults bear brunt of disease burden
  2/3 of complications occur in ≥ 50 years
  Usually less severe in children / younger adults

Complications include:

  Common: Postherpetic neuralgia (PHN), scarring
  Less common: bacterial superinfection, motor neuron palsies
  Rare: pneumonia, encephalitis, stroke, Ramsey Hunt syndrome, hearing loss

Ophthalmic zoster - 10-25% of pts; can result in facial scarring & loss of vision

NHMRC Australian Immunisation Handbook 10th Ed 2013;
Harpaz et al MMRW 2008;
Everyone who has had chickenpox is at risk of shingles

97% of Australians over 30 are at risk

~1 in 3 adults will develop shingles in their lifetime

50+
Risk increases with age, particularly after 50

It’s all about prevention of pain

Viral replication causes inflammation / injury to the nerve

Damage begins before the rash appears

Pain varies in nature and can be constant or intermittent

Can be triggered by mild, non-noxious stimulation (e.g. clothing)

May persist for months or even years
Postherpetic neuralgia (PHN)

Prolonged pain that persists 4-6 weeks after crusting of vesicles

Most frequent debilitating complication of shingles

10% of all pts, up to 75% in those over 70yo

Lasts an average of 3.5 years
PHN - difficult to prevent & treat

Antiviral therapy –
If started within 72 hrs of rash onset reduces severity/duration of shingles, but less impact on PHN

Variety of pain medications
Paracetamol, Opiates, amitriptyline, gabapentin, pregabalin
Other serious complications

Ophthalmic zoster

Occurs in 10-25% of shingles cases
May cause facial scarring & visual loss

Stroke Risk

Shingles seems to increase risk of stroke in the following 6 months
(63% higher risk in the 4 weeks after shingles vs. baseline period)

Live zoster vaccine
Contains live, attenuated varicella zoster virus (Oka/Merck)

Zoster & Varicella vaccines are not identical
- zoster vaccine more potent

Higher potency required to achieve the immune response necessary to prevent shingles

Varicella vaccine wont prevent shingles in older people & Zoster vaccine too potent for kids
Zoster vaccine - indications

Prevention of shingles in people 50+
Postherpetic neuralgia (PHN) and for reduction of acute and chronic zoster-associated pain in individuals 60+

Not a treatment for shingles or PHN
Protective efficacy - decreases with age

50-59yrs  70%
60-69yrs  64%
>70yrs    38%

Oxman MN et al. NEJM 2005; 352:2274-84
Protection is durable

![Graph showing protection durability over time](chart.png)

Percent of subjects with zoster

Time since the start of follow-up (in years)

- **Zostavax**
- **Placebo**

*p < 0.001*

* A limited number of subjects were followed beyond year 4
So not surprisingly protects against PHN

Zoster vaccine vs. placebo (adults ≥60yo)

**Diagram Description:**
- **Y-axis:** Number of shingles cases with PHN
- **X-axis:** Placebo vs. Zoster Vaccine
- **Placebo:** (n=19,247) with 80 cases of PHN
- **Zoster Vaccine:** (n=19,254) with 27 cases of PHN
- **Protection Efficacy:** 67% (95% CI 48-79%) vs. placebo
Kaplan-Meier plot of the cumulative incidence of PHN over time* in the shingles prevention study

PHN = postherpetic neuralgia

* A limited number of subjects were followed beyond year 4
Zoster associated pain severity-by-duration score over time in the shingles prevention study*

* The inset presents the number of subjects with severity-by-duration score > 600. For example, a daily worst pain rated at the maximum score of 10 for > 60 days would result in a severity-by-duration score of > 600
Zoster vaccine - Live vaccine

C/I in immunosuppressed

Primary & acquired immunodeficiency states
  e.g. leukemia, lymphoma, bone marrow or lymphatic dysfunction, immunosuppression due to HIV/AIDS, cellular immune deficiencies

Immunosuppressive therapy
  e.g. chemotherapy, radiation therapy, high-dose corticosteroids

Active untreated tuberculosis

Pregnancy
Not immunocompromised

Steroids

- <10 mg prednisolone
- >1 month since high-dose (≥10 mg pred daily for >2 weeks)
- Maintenance physiologic doses
- Inhaled / Topical / Intra-articular, bursal, or tendon injection

Autoimmune (eg SLE, IBD, RA, MS) but not on immunosuppressives

HIV: Normal CD4, controlled virus

Cancer: ≥3 months since chemo & in remission

BMTx: >2 yrs post Tx, not on immunosuppressives, no GVHD
NHMRC Immunisation Handbook (10th Edition)
Australian and New Zealand Society for Geriatric Medicine:

- Single dose of zoster vaccine for adults ≥60 years
- C/I in persons with significant immunocompromise

Generally well tolerated

Evaluated for safety in more than 32,000 adults aged $\geq 50$ years

Side effects

Injection site reactions - most common
- Erythema, pain/tenderness, swelling, pruritus - very common in clinical trials
- More likely in adults aged 50–59 years than in those $\geq 60$ years

Headache & fatigue are the most frequent systemic side effects

Over 21 million doses distributed worldwide since 2006
- Postmarketing studies support safety profile seen in clinical trials

ZOSTAVAX PI; Schmader et al CID 2012; Data on file; Baxter et al Vaccine 2012; Tseng et al Journal of Internal Medicine 2012
Compatibility with other vaccines

Influenza - can be co administered
   No impact on either vaccine; separate injections at different sites

But

Pneumovax - should **not** be given concomitantly
   Safe, but reduced efficacy of Zoster vaccine - give at least 4 weeks apart
Zoster vaccine - single dose given subcutaneously

Individuals 50+ should receive a single dose (0.65mL) of vaccine SC

Efficacy lasts 8-10 years

Studies to further understand duration of protection are ongoing

Revaccination/ boosters?

Need has not been determined

Zoster vaccine available for adults aged 50+ who wish to be vaccinated

Private prescription

$ 230-250

Will be subsidised through NIP from Nov 2016 in persons aged 70-79
If a patient can’t remember having chickenpox, should they be vaccinated against Zoster?

Most older Australians are seropositive (97%)

Not worth checking serology prior to administration of Zoster vaccine!
Recent shingles?

Unclear

NHMRC Immunisation Handbook:
“vaccine could be given at least 1 year after the shingles episode”
WANTED
DEAD OR ALIVE
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., Roman Chlibek, M.D., Ph.D., Javier Diez-Domingo, M.D., Ph.D., Shinn-Jang Hwang, M.D., Myron J. Levin, M.D., Janet E. McElhaney, M.D., Airi Poder, M.D., Joan Puig-Barberà, M.D., M.P.H., Ph.D., Timo Vesikari, M.D., Ph.D., Daisuke Watanabe, M.D., Ph.D., Lily Weckx, M.D., Ph.D., Toufik Zahaf, Ph.D., Thomas C. Heineman, M.D., Ph.D., for the ZOE-50 Study Group

N Engl J Med
Volume 372(22):2087-2096
May 28, 2015
Recombinant subunit vaccine

VZV glycoprotein (main target of immune response to VZV)
Proprietary adjuvant system

Previous studies - good immune response lasting >3 years
RCT

15,000 participants

50 years of age or older

Varicella–zoster virus subunit vaccine with AS01B adjuvant

2 doses 1 month apart
16,160 Participants were enrolled

749 Were excluded
- 726 Had Good Clinical Practice violation
- 23 Did not receive vaccine

15,411 Underwent randomization

Total Vaccinated Cohort

7698 Were assigned to receive vaccine dose 1 (month 0)

7713 Were assigned to receive placebo dose 1 (month 0)

Reactogenicity Subgroup

4460 Completed diary cards

4466 Completed diary cards

337 Did not receive dose 2

277 Did not receive dose 2

7361 Received dose 2 (month 2)

7436 Received dose 2 (month 2)

17 Were excluded
- 4 Did not receive vaccine according to protocol
- 9 Received wrong vaccine
- 4 Had diagnosis of HZ <30 days after dose 2

21 Were excluded
- 2 Did not receive vaccine according to protocol
- 5 Received wrong vaccine
- 14 Had diagnosis of HZ <30 days after dose 2

Modified Vaccinated Cohort

7344 Were included in modified vaccinated cohort

7415 Were included in modified vaccinated cohort
## Table 1. Characteristics of the Participants at Baseline (Total Vaccinated Cohort). *

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HZ/su Group (N=7698)</th>
<th>Placebo Group (N=7713)</th>
<th>All Participants (N=15,411)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (±SD) at first dose</td>
<td>62.4±9.0</td>
<td>62.3±9.0</td>
<td>62.3±9.0</td>
</tr>
<tr>
<td>Age group — no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex — no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>4711 (61.2)</td>
<td>4713 (61.1)</td>
<td>9,424 (61.2)</td>
</tr>
<tr>
<td>Male</td>
<td>2987 (38.8)</td>
<td>3000 (38.9)</td>
<td>5,987 (38.8)</td>
</tr>
<tr>
<td>Race — no. (%)†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>5532 (71.9)</td>
<td>5535 (71.8)</td>
<td>11,067 (71.8)</td>
</tr>
<tr>
<td>Black</td>
<td>140 (1.8)</td>
<td>130 (1.7)</td>
<td>270 (1.8)</td>
</tr>
<tr>
<td>Asian</td>
<td>1466 (19.0)</td>
<td>1470 (19.1)</td>
<td>2,936 (19.1)</td>
</tr>
<tr>
<td>Other</td>
<td>560 (7.3)</td>
<td>578 (7.5)</td>
<td>1,138 (7.4)</td>
</tr>
<tr>
<td>Region — no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asia or Australia</td>
<td>1642 (21.3)</td>
<td>1642 (21.3)</td>
<td>3,284 (21.3)</td>
</tr>
<tr>
<td>Europe</td>
<td>3941 (51.2)</td>
<td>3948 (51.2)</td>
<td>7,889 (51.2)</td>
</tr>
<tr>
<td>Latin America</td>
<td>772 (10.0)</td>
<td>779 (10.1)</td>
<td>1,551 (10.1)</td>
</tr>
<tr>
<td>North America</td>
<td>1343 (17.4)</td>
<td>1344 (17.4)</td>
<td>2,687 (17.4)</td>
</tr>
</tbody>
</table>

* There were no significant differences between the groups.
† Race was self-reported.
Table 2. Vaccine Efficacy against the First or Only Episode of Herpes Zoster Infection.*

<table>
<thead>
<tr>
<th>Cohort and Age Group</th>
<th>HZ/su Group</th>
<th>Placebo Group</th>
<th>Vaccine Efficacy†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rate of</td>
<td>Rate of</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Herpes</td>
<td>Herpes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Zoster</td>
<td>Zoster</td>
<td></td>
</tr>
<tr>
<td></td>
<td>no./1000</td>
<td>no./1000</td>
<td></td>
</tr>
<tr>
<td></td>
<td>person-yr</td>
<td>person-yr</td>
<td></td>
</tr>
<tr>
<td>Modified vaccinated cohort</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All participants in cohort</td>
<td>0.3</td>
<td>9.1</td>
<td>97.2 (93.7–99.0)</td>
</tr>
<tr>
<td>50–59 yr</td>
<td>0.3</td>
<td>7.8</td>
<td>96.6 (89.6–99.3)</td>
</tr>
<tr>
<td>60–69 yr</td>
<td>0.3</td>
<td>10.8</td>
<td>97.4 (90.1–99.7)</td>
</tr>
<tr>
<td>70 yr or older</td>
<td>0.2</td>
<td>9.4</td>
<td>97.9 (87.9–100.0)</td>
</tr>
</tbody>
</table>

Vaccine efficacy 97-98%
## High incidence of minor side effects

<table>
<thead>
<tr>
<th></th>
<th>Vaccine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Local site reactions</strong></td>
<td>81%</td>
<td>12%</td>
</tr>
<tr>
<td><strong>Systemic reactions</strong></td>
<td>66%</td>
<td>29%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>46%</td>
<td>12%</td>
</tr>
<tr>
<td>Fever</td>
<td>21%</td>
<td>3%</td>
</tr>
<tr>
<td>Headache</td>
<td>39%</td>
<td>16%</td>
</tr>
<tr>
<td>Shivering</td>
<td>28%</td>
<td>6%</td>
</tr>
</tbody>
</table>

But NO difference in SAEs or death
Conclusions

HZ/su vaccine significantly reduced zoster in adults ≥50 yo

Efficacy in adults > 70 yo similar to younger pts
What we don’t know:

Safety & efficacy in immunosuppressed

Longevity of protection

Interplay bn live & subunit vaccine

Watch this space…..
Thank you