Herpes Zoster & Postherpetic Neuralgia

Robert W. Johnson, MD.,FRCA.

Bristol, UK.
Is there a need?
Will the need change?
Does vaccination satisfy the need?
Will the public seek/want it?
Is it cost effective?

At least the vaccine will not encourage sexual promiscuity!!
Topics

- The varicella zoster virus
- Primary & secondary infection
- Epidemiology & anticipated change
- VZV immune mechanisms
- Cost of HZ and PHN
- PHN – prediction, mechanisms & management
- Vaccination against HZ
- Cost effectiveness of HZ vaccine
Varicella Zoster Virus (VZV)

- Primary infection
  - Varicella

- Persistence with clinical latency

- Reactivation
  - Herpes zoster
Diagnosis of HZ

- **Clinical diagnosis**
  - Up to 20% error rate
  - Most common confusion – HSV
    (cold sores, genital herpes, MI, cholecystitis)

- **Laboratory diagnosis**
  - Usually unnecessary
  - PCR
  - Culture

HZ & PHN – the problems …

- HZ is common with greater incidence in older adults and immunocompromised individuals: ~3% hospitalized

- PHN is the most common complication of HZ

- Other, serious, complications are more rare

- HZ & PHN are costly to the individual and society

- Until now no preventive strategy for HZ

Dworkin RH, Johnson RW., Breuer J et al. Management of herpes zoster. CID 2007:44(Suppl 1);S1-S25

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Who gets Herpes Zoster?

- Normal older adults
  - Immunesenescence

- Immunocompromised individuals
  - Malignancy & its treatment
    - Lymphoma
    - Chemotherapy, radiotherapy
  - Immunocompromising disease
    - HIV
  - Therapeutic immune suppression
    - Organ transplant
    - Steroids etc.

- Normal children and younger adults


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Age related incidence of HZ and PHN

Rate per 1000 per year

Age (years)

0 10 20 30 40 50 60 70 80+

Zoster

PHN

Hope-Simpson RE. J R Coll Gen Pract. 1975; 25:571-575

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Incidence and absolute numbers of Herpes Zoster (EU 25)

# Cases

<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+</th>
</tr>
</thead>
<tbody>
<tr>
<td>EU cases</td>
<td>300000</td>
<td>200000</td>
<td>150000</td>
<td>100000</td>
<td>50000</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Annual rate/1000 person-yrs</td>
<td>12,00</td>
<td>10,00</td>
<td>8,00</td>
<td>6,00</td>
<td>4,00</td>
<td>2,00</td>
<td>0,00</td>
<td>0,00</td>
<td>0,00</td>
</tr>
</tbody>
</table>

Proportion of Patients with PHN by age group

Epidemiology and management costs of Herpes Zoster (HZ) and Post-Herpetic Neuralgia (PHN) in the UK. Remy et al

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The future …

- Population demography
- Disease and its treatment
- Antiviral drugs
- Varicella vaccine
- Herpes zoster vaccine
European population distribution by age: population pyramids

Source: UN World Population Ageing: 1950–2050
Facts about ageing

- Social and medical advances have added ‘years to life’ but not ‘life to years’
- Short-term debility leads to prolonged detriment to ADL and independence
- Zoster-specific CMI declines with advancing age
- Neurosenescence may add to PHN susceptibility
Reported varicella cases and vaccination coverage* by year -- Varicella Active Surveillance Project, 1995-2005

**Antelope Valley**

**West Philadelphia**

*Coverage estimates from NIS in LA and Philadelphia, among children 19-35 months of age.*

Hypothesis - effects of vaccination strategies on HZ

- Infant vaccination
- Targeted vaccination


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Lifetime changes in immune status

Prediction of PHN risk

- Baseline and follow up data from 965 HZ patients examined by univariate and multivariate analysis confirmed that:
  - Older age
  - Female gender
  - Presence of prodrome
  - Greater rash severity
  - Greater acute pain severity
  - (Diabetes)

made independent contributions to predicting which patients developed PHN

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What do antivirals achieve?

- Reduce acute pain
- Accelerate rash healing
- Reduce period of viral shedding
- Reduce duration of pain
- Effect on complications other than pain
- Excellent safety profile
- Reduction in overall burden of HZ
Cost of HZ – 1st 6 months

- Societal and economic burden
- Prospective observational pilot study
- 70 patients had detailed follow-up
- Average overall cost 1st 6 months £524 (min 20, med 158, max 4218)
- Medical costs highest >65
- Societal costs highest <65

Mean cost per PHN episode by severity

Proportion of herpes zoster patients developing post-herpetic neuralgia and its management in the UK. Gauthier et al

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Proportion of management costs of HZ and PHN by category

Epidemiology and management costs of Herpes Zoster (HZ) and Post-Herpetic Neuralgia (PHN) in the UK. Remy et al

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Facts about PHN

- Antiviral drugs (+/- steroids) have limited effect in prevention of PHN: they do not ‘bring dead neurons back to life’
- Nerve blocks or neuropathic pain drugs: evidence for PHN prevention limited - lacking in practicality
- Despite significant advances <50% of PHN patients gain 50% pain relief
Sources of Neuropathic Pain

- Tic douloureux
- HIV-associated pain
- Poststroke pain
- Phantom pain (postamputation)
- Multiple sclerosis
- Causalgia or reflex sympathetic dystrophy
- Spinal cord injury
- Cancer-related pain
- Postherpetic neuralgia
- Diabetic neuropathy
- Low back pain

US prevalence (millions of cases)


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Agents with NNT < 5

- M-prednisolone (1.t)
- Aspirin (topical)
- Lidocaine 5% patch
- TCAs
- Strong opioids
- Capsaicin
- Gabapentin
- Tramadol
- Pregabalin

NNT (50%)

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Hempenstall et al 2005. Based on systematic review of RCTs with a Jadad score ≥ 3
Management Plan for HZ & PHN

- **Herpes Zoster**
  - Early antiviral therapy
  - Early neuropathic pain treatment (e.g., Amitriptyline/Gabapentin)

- **Postherpetic Neuralgia**
  - Antidepressants (e.g., Amitriptyline)
  - Anticonvulsants (Gabapentin, Pregabalin)
  - Opioids (Tramadol, Oxycodone, Morphine)
  - Topicals (Lidocaine, Capsaicin)

- **Children**
  - Vaccination

- **Adults**
  - Vaccination
Prevention of Herpes Zoster by vaccination

- Reduction in number of susceptible individuals in population
  - Varicella vaccine

- Increased VZV-specific CMI of seropositive individuals
  - Relevance of exogenous boosting
  - HZ vaccine

- Unlike other vaccine-preventable diseases, HZ not directly related to exposure to exogenous infective agent

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Rationale for vaccination against HZ
The Oka vaccine

• Live, attenuated, cell-free preparation of Oka strain VZV (killed virus antigen weak stimulant of CMI)

• Original ‘wild type’ virus isolated by Michiaki Takahashi from 3 year old Japanese child whose family name was Oka

• Three licensed preparations – Merck (stored at -15ºC), GSK (stored at 2ºC) and Merck (refrigerated)

• The same strain of Merck/Oka virus is used for varicella and herpes zoster protection BUT the latter contains a several fold greater (14x) titer of virus because of the reduced immune response of older adults
A Vaccine to Prevent Herpes Zoster and Postherpetic Neuralgia in Older Adults

Shingles Prevention Study

**Objective**

- To determine whether immunization with a live attenuated zoster vaccine can reduce the incidence and/or severity of HZ and PHN in persons ≥60 years of age.
Shingles Prevention Study

Design

- Randomized, double-blind, placebo controlled trial
- 38,546 subjects
- Stratified by age group: 60 - 69 yr and >70 yr
- Active vaccine or placebo vaccine
Shingles Prevention Study

- **Participants**
  - Immunocompetent adults greater than 60 years old who had no prior history of herpes zoster
  - History of varicella or ≥30 years residence in US
  - Included male and female veterans and non-veterans
  - Sample size estimate = 37,200 (18,600 each group) for 95% power, \( \alpha = 0.05 \) (two-sided), to detect 60% reduction in herpes zoster BOI score

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Incidences of HZ and PHN

- PHN – worst pain and discomfort $\geq 3$ (0-10 scale) 90 or more days from rash onset
  - $V_{E_{PHN}} = 1 - (PHN \text{ incidence vaccine/PHN incidence placebo})$

- HZ
  - $V_{E_{HZ}} = 1 - (HZ \text{ incidence vaccine/HZ incidence placebo})$
Summary of results

HERPES ZOSTER VACCINE:

- Reduces HZ Pain BOI by 61% *


*p<0.001 versus placebo

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Burden of Illness (BOI)

- Population measure
- Sensitive to the incidence, duration and severity of HZ pain over 6 months

Severity-by-duration (AUC) calculated for each HZ case

Subjects without HZ were assumed to have no HZ-associated pain (i.e., AUC=0)
HERPES ZOSTER VACCINE:

- Reduces HZ Pain BOI by 61% *
- Prevents HZ by 51% *
- Prevents PHN by 67% *
- Elicits a VZV-specific CMI response

* p< 0.001 versus placebo


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ZO斯塔瓦克斯™ 的效力随年龄变化

- HZ
- PHN
- BOI

年龄段：
- 60 至 69 岁
- ≥70 岁

95% CI

疫苗效力（%）

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Safety

- Serious Adverse Events (whole study population): Number and type of event similar in vaccine and placebo groups.
- SAE (safety sub-study) higher in vaccine (1.9%) than placebo (1.5%) group - RR 1.5 (95%CI=1.0-2.3).
- No temporal or clinical patterns of adverse events in vaccine recipients to suggest a causal relationship.
- Death and hospitalization similar in both groups throughout.
Safety

- Mild local & systemic reactions:
  - Injection site erythema, swelling, pain etc 48.3% in vaccine group & 16.6% with placebo (p<0.05): risk higher in younger cohort
  - Headaches etc slightly more common in vaccine recipients
  - Risk of fever similar in both groups
Cost-effectiveness

- 5 studies have estimated cost-effectiveness of 1 dose vaccination ≥60yr
- At vaccine cost of US$150: -
  - $27,000 – 112,000 per QALY
  - WHO threshold = 3x gross domestic product per capita = $94,431 for US
  - Appears acceptable in comparison to other interventions but at intermediate-to-high end of range
Advice at this time

- Vaccinate against HZ at age 50 to 60
- In patients who develop HZ:
  - Antiviral drugs (preferably pro-drug)
  - Effective analgesia
  - Early use of TCA / pregabalin / strong opioids if required
Summary

HERPES ZOSTER VACCINE

- Reduces HZ Pain BOI by 61% *
- Prevents HZ by 51% *
- Prevents PHN by 67% *
- Elicits a VZV-specific CMI response
- Has an excellent safety profile
- Efficacy for HZ & PHN endpoints was demonstrated through 48 months of follow-up

* p< 0.001 versus placebo

Efficacy on HZ Burden of Illness (BOI)

- **HZ BOI** = Incidence x severity x duration of HZ associated pain
- Similar HZ Vaccine Efficacy when results stratified according to sex or age

**EFFICACY = 61.1%**
(95% CI 51.1 - 69.1%)

* p< 0.001 versus placebo

HZ Burden of Illness (BOI) Score

- Herpes zoster BOI Score is the average Area-Under-the-Curve (AUC) of zoster pain of all individual randomized subjects in a group of subjects (e.g., vaccine recipients) for 6 months.

  - Subjects who do not develop herpes zoster are assigned a score of 0.

- Vaccine efficacy for BOI defined as relative reduction in BOI score in vaccine vs. placebo group.

  - \[ VE_{BOI} = 1 - \frac{\text{BOI score vaccine}}{\text{BOI score placebo}} \]
**Efficacy on HZ**

- **HZ case definition** = PCR+ or Culture + or CEC+

Vaccine Efficacy on HZ incidence

- **EFFICACY = 51.3%**
  (95% CI 44.2 - 57.6%)

- **p< 0.001 versus placebo**

**HZ Vaccine Efficacy greater among 60-69 year old subjects**
**than subjects > 70 years (64% versus 38%, p<0.001)**

Efficacy on PHN incidence

PHN = presence of pain (score 3 on 0-10 scale) beyond 90 days after HZ rash onset

![Graph showing vaccine efficacy on PHN incidence]

- **Vaccine Efficacy on PHN incidence**
  - Placebo: 1.38
  - Vaccine: 0.46
  - **EFFICACY = 66.5%**
  - (95% CI 47.5 - 79.2%)
  - *p < 0.001 versus placebo

- Cases of PHN: HZ vaccine group: 27 versus Placebo group: 80
- Similar HZ Vaccine Efficacy when results stratified according to sex or age

*M.N. Oxman et al, N Engl J Med, 2005 Jun 2; 352 (22): 2271-84*
Shingles Prevention Study

- **Intervention**
  - 0.5 ml live, attenuated zoster vaccine (Oka/Merck) or placebo s.c. in non-dominant arm
Study Subjects

Enrolled 38,546

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%)

## Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Vaccine Group (N=19,270)</th>
<th>Placebo Group (N=19,276)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age ≥70 yr</strong></td>
<td>8,892 (46.1%)</td>
<td>8,907 (46.2%)</td>
</tr>
<tr>
<td><strong>Sex – Female</strong></td>
<td>7,867 (40.8%)</td>
<td>7,919 (41.1%)</td>
</tr>
<tr>
<td><strong>Race – White</strong></td>
<td>18,393 (95.4%)</td>
<td>18,381 (95.4%)</td>
</tr>
<tr>
<td><em><em>Health Limits</em> No</em>*</td>
<td>9,924 (51.5%)</td>
<td>9,862 (51.2%)</td>
</tr>
<tr>
<td><strong>Mild</strong></td>
<td>7,440 (38.6%)</td>
<td>7,423 (38.5%)</td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
<td>1,637 (8.5%)</td>
<td>1,714 (8.9%)</td>
</tr>
<tr>
<td><strong>Severe</strong></td>
<td>266 (1.4%)</td>
<td>273 (1.4%)</td>
</tr>
</tbody>
</table>

*Health-related limitations on activities

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Adapted from Table 1 in Oxman et al. NEJM. 2005;352:2271-84
Sub-study populations

- Safety sub-study (n = 6616)
  - At all 22 study sites
  - Detailed safety assessment
    - Completed a vaccination report card through Day 42 post-vaccination
    - Followed for hospitalizations until the end of study

- CMI sub-study (n = 1395)
  - At 2 study sites
  - Specimens were obtained at baseline and post-vaccination (6 weeks; 1, 2 and 3 years)
    - Antibody level by gpELISA
    - VZV-specific CMI by ELISPOT and RCF assays
Efficacy analysis population

- Modified Intention-To-Treat population (MITT)
  - All enrolled subjects who did not develop evaluable HZ within 30 days post-vaccination
  - Analyses included only the first confirmed case

- Why exclude cases in the first 30 days?
  - Cases may have been in development at the time of vaccination
  - Vaccine-induced immune responses unlikely to be fully developed for some time after vaccination
  - Potential confusion with vaccine-induced rash

Confirmation of HZ cases

Suspected cases of HZ
1,308

VZV Vaccine
481

Not a confirmed case of HZ
156 Not HZ
3 Not seen until after crusting

Confirmed cases of HZ (ITT)
322

Excluded from MITT
6 HZ within 30 days of vaccination
1 second episode of HZ

315 confirmed cases of HZ (MITT)
294 VZV positive, PCR
2 VZV positive, local culture
19 HZ by Clin. Eval. Committee

Placebo
827

Not a confirmed case of HZ
161 Not HZ
4 Not seen until after crusting

Confirmed cases of HZ (ITT)
662

Excluded from MITT
18 HZ within 30 days of vaccination
2 second episode of HZ

642 confirmed cases of HZ (MITT)
600 VZV positive, PCR
8 VZV positive, local culture
34 HZ by Clin. Eval. Committee

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Histogram of Severity-by-Duration Score (AUC) of HZ Pain Among Evaluable HZ Cases by Vaccination Group (MITT Population)

HZ-Associated Pain Severity-by-Duration Score (AUC)

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Efficacy on all HZ severe cases

HZ severe cases = HZ with severe x duration pain score > 600

Vaccine efficacy on severe HZ cases

EFFICACY = 73%
(95% CI 46 - 87.6%)
SPS Safety Evaluation

- **All Subjects**
  - All adverse events recorded within 42 days after vaccination
  - Subjects contacted at end of 42 day period and prompted for any other unreported adverse events
  - Deaths identified by reports from family and during follow-up of missed monthly calls
## Serious Adverse Events Among All Subjects

<table>
<thead>
<tr>
<th>Event</th>
<th>Vaccine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Subjects</td>
<td>19,270</td>
<td>19,276</td>
</tr>
<tr>
<td><em>Day of Vaccin. To Study End</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>218 (2.1%)</td>
<td>246 (2.4%)</td>
</tr>
<tr>
<td>Vaccine-related SAE</td>
<td>2 (&lt;0.1%)</td>
<td>3 (&lt;0.1%)</td>
</tr>
<tr>
<td><em>Day of Vaccin. To Day 42</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>14 (0.1%)</td>
<td>16 (0.1%)</td>
</tr>
<tr>
<td>≥1 SAEs</td>
<td>255 (1.4%)</td>
<td>254 (1.4%)</td>
</tr>
</tbody>
</table>

Adapted from Table 4 in Oxman et al. NEJM 2005;352:2271-84
SPS Safety Evaluation

- **Adverse Events Substudy**
  - Approximately 300 subjects per site enrolled
  - During 42 days after vaccination, daily log of body temperature and vaccination report card of clinical symptoms and injection site complaints
  - During remainder of study, followed by monthly calls and site personnel to identify all hospitalizations
Safety (AEs sub-study)

Day of vaccination to Day 42

Injection site AEs

- Vaccine – 3,345 Subjects
- Placebo – 3,271 Subjects

Systemic AEs ≥ 1

- Vaccine – 23.6%
- Placebo – 24.7%

# Rate of HZ Complication
(MITT Population)

<table>
<thead>
<tr>
<th></th>
<th>ZOSTAVAX™</th>
<th>Placebo</th>
<th>% Relative Reduction in ZOSTAVAX™ Recipients (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=19,270</td>
<td>N=19,276</td>
<td></td>
</tr>
<tr>
<td>Neurologic†</td>
<td>n</td>
<td>Incidence Rate*</td>
<td>n</td>
</tr>
<tr>
<td></td>
<td>29</td>
<td>0.5</td>
<td>82</td>
</tr>
<tr>
<td>Cutaneous</td>
<td>39</td>
<td>0.7</td>
<td>116</td>
</tr>
<tr>
<td>Ocular involvement</td>
<td>14</td>
<td>0.2</td>
<td>40</td>
</tr>
<tr>
<td>Sacral dermatome</td>
<td>6</td>
<td>0.1</td>
<td>24</td>
</tr>
<tr>
<td>involvement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visceral complications</td>
<td>9</td>
<td>0.2</td>
<td>28</td>
</tr>
</tbody>
</table>

* Incidence rate = per 1000 person years (total population).
† Excluding pain.

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Cost-effectiveness of HZ vaccine in USA

- Age-specific analytic model
- Lifetime costs and outcomes for HZ, PHN, other HZ complications
- Vaccinated and non-vaccinated cohorts aged ≥ 60 years
- Societal and payer perspectives considered

Pellissier JM et al. *Vaccine* 25 (2007);8326-8337
For 1,000,000 US vaccine recipients ≥60 ...

- HZ vaccine would eliminate:
  - 75,548-88,928 cases of HZ
  - >20,000 cases of PHN
  - >300,000 outpatient visits
  - >375,000 prescriptions
  - >97,000 ER visits
  - >10,000 hospitalizations

- Saving US$ 82-103 million annually

Pellissier JM et al. *Vaccine* 25 (2007);8326-8337
Cost-effectiveness of HZ vaccination in US

- US$ 16,229 - 27,609 per QALY gained depending on data source and analytic perspective.

- Most sensitive to:
  - PHN costs
  - Duration of vaccine efficacy
  - Complication costs
  - QALY loss associated with pain

Pellissier JM et al. Vaccine 25 (2007);8326-8337
Cost-effectiveness and QALYs

- US$ 50,000 – 100,000 per QALY gained considered cost-effective

- WHO suggests 3 X domestic product/capita = 3 X £20,000 = £60,000 for UK

- For comparison:
  - Hypertension management US$ 60,000/ QALY gained
Cost-effectiveness results in the 65+ UK population
(40% coverage rate)

<table>
<thead>
<tr>
<th>Results</th>
<th>Vac Policy</th>
<th>No Vac Policy</th>
<th>Difference</th>
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<tbody>
<tr>
<td>Costs</td>
<td>£505,521,469</td>
<td>£159,097,028</td>
<td>£346,424,441</td>
</tr>
<tr>
<td>Effectiveness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QALYs</td>
<td>74,061,721</td>
<td>74,031,587</td>
<td>30,134</td>
</tr>
<tr>
<td>HZ Cases</td>
<td>634,725</td>
<td>779,603</td>
<td>144,878</td>
</tr>
<tr>
<td>PHN Cases</td>
<td>133,945</td>
<td>184,028</td>
<td>50,083</td>
</tr>
<tr>
<td>ICERS</td>
<td></td>
<td></td>
<td>£11,496</td>
</tr>
<tr>
<td>Cost per QALY gained</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost per HZ Case Avoided</td>
<td></td>
<td></td>
<td>£2,391</td>
</tr>
<tr>
<td>Cost per PHN Case Avoided</td>
<td></td>
<td></td>
<td>£6,917</td>
</tr>
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</table>
## Mean cost per case of HZ over 6-month follow-up by age

<table>
<thead>
<tr>
<th>Age class</th>
<th>Sample size</th>
<th>Patient (£)</th>
<th>NHS (£)</th>
<th>Society (£)</th>
<th>Total (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;65 years</td>
<td>45</td>
<td>10.8 (0, 4, 187)</td>
<td>85.6 (20, 68, 696)</td>
<td>430.0 (0, 26, 3265)</td>
<td>526.3 (20, 173, 3578)</td>
</tr>
<tr>
<td>65+ years</td>
<td>25</td>
<td>42.5 (0, 0, 1000)</td>
<td>400.9 (48, 138, 3257)</td>
<td>76.6 (0, 0, 957)</td>
<td>519.9 (48, 138, 4218)</td>
</tr>
<tr>
<td>Overall</td>
<td>70</td>
<td>22.1 (0, 1, 1000)</td>
<td>198.2 (20, 86, 3257)</td>
<td>303.8 (0, 0, 3267)</td>
<td>524.0 (20, 158, 4218)</td>
</tr>
</tbody>
</table>

The minimum, median and maximum costs are in ()

Follow up: 146 GP consultations, 7 hospital visits, 6 emergency ambulances, 4 admissions, 6 consultations with complementary practitioners, 307 days work lost by patients, 52 by carers
The future

- Duration of protection
- Need for booster injection(s)
- Effects in the elderly ‘unfit’ patient
- Vaccine suitable for immunocompromised patients
- Reduced prevalence of seropositive individuals
- More effective vaccine?
  - n.b. effectiveness of other vaccines in elderly adults