Herpes Zoster: Addressing the burden of illness

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Presenter disclosure

- Presenter’s name: Rosemarie Patodia
- I have no current or past relationships with commercial entities
- Speaking fees for current program:
  - I have received a speaker’s fee from Pear Education for this learning activity
Commercial support disclosure

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Learning objectives

After completion of this educational workshop, pharmacists should be better able to:

1. Describe the pathogenesis, epidemiology and symptoms of herpes zoster
2. Describe how burden of illness is assessed, and review the burden of illness associated with herpes zoster
3. Discuss the reduction in burden of illness and cost-effectiveness associated with herpes zoster vaccine use
4. Recommend herpes zoster vaccine for individuals meeting indications for use, based on evidence of efficacy, effectiveness and safety
Herpes Zoster (HZ): Overview

• AKA “shingles” – reactivation of varicella-zoster virus (“chickenpox”)
  – Latent in sensory ganglia since time of primary infection
• Common complication is postherpetic neuralgia (PHN)
  – Clinically significant pain persisting > 90 days after rash onset
  – Pain is most debilitating symptom of herpes zoster
• Additional complications may include:
  – Disseminated zoster
  – Ophthalmic zoster
  – Motor paresis (including facial paralysis)
  – Inflammation of spinal cord and brain

HZ: Epidemiology

• ~20-35% of population in developed countries at some time in life (incidence has been increasing)\(^1\)
• Unvaccinated persons who live to 85 years have 50% risk\(^2\)
• Complications in 13-40% of cases\(^1\)
  – PHN in 8-27% with HZ
  – ↑ with age – 4 x higher in > 70 yrs vs < 60 yrs
  – Up to 3% require hospitalization

Anyone ever infected with varicella is at risk for herpes zoster

- The key risk factor is advancing age\(^1,2\)
  - >2/3 of cases occur in people >50 years of age\(^3\)
- Other risk factors: immunocompromised,\(^1\) COPD\(^4\)
- Possible factors: female sex, non-black race, infrequent varicella exposure, inflammatory disease\(^5\)

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Why is incidence of HZ increasing?

Hypotheses include:

1. Aging population
2. Increasing numbers of immunocompromised individuals
3. Decreasing exposure to childhood varicella - reduces incidence of “booster” of immunity compared to previous populations.

HZ: the warning signs

- Rash is often preceded by burning, tingling, itching, shooting sensation and/or pain for 4 to 6 days before rash onset
- Mean pain severity 6 out of 10
- Symptoms may be continuous or episodic
- Diagnosis can only be made once the characteristic rash appears
  - However, prodromal signs alert to watch for disease onset signs and allow for early treatment

HZ: the symptoms

• Typically appears as rash that is unilaterally localized in a region affecting up to 3 adjacent dermatomes

• Rash cycles through lesions usually in first 96 hours of rash, usually accompanied by pain

• Lesions turn into erythematous maculopapules, then to vesicles and pustules, in varying stages over 3-5 days

HZ: the symptoms

- Pustules usually crust within 10 days
- Crusted lesions last ~ 1-2 weeks (this stage usually longer in older individuals)
- Cutaneous healing for 2-4 weeks

The pain associated with acute HZ1

- May be intermittent or constant, can be disabling
- Often described as burning, itching, shooting or throbbing sensation
- Allodynia (pain in response to normally non-painful stimulus) in area of rash
- Pain usually disappears with rash but may persist for several weeks, months, or years in some

PHN symptoms

- Pain persisting for months to years after rash resolution (begins about a month or so later)
- Mild to excruciating chronic pain
- May affect sleep, mood, work, activities of daily living
- May result in social withdrawal and depression

Selected complications

- Secondary bacterial superinfection

- Neurologic complications

- Eye complications (herpes zoster ophthalmicus) may include permanent visual impairment


What is “burden of illness”?1

• Direct and indirect costs
  • Direct costs include:
    – Hospital care and other institutions
    – Physician care and other health professionals
    – Drug expenditures
    – Capital, public health spending
  • Indirect costs include:
    – Lost production due to injury, illness, or death

Herpes zoster burden of illness

- Systematic literature review
- All concur that HZ is widespread disease with heavy social and economic burden

MASTER Study

- Objective to gain thorough understanding of burden of illness of HZ and PHN
- 261 outpatients with HZ, age ≥ 60 years
- Median pain duration 32.5 days
- Predictors of increased severity of illness:
  - Higher pain severity at recruitment, more lesions, lower income and immunocompromise

Estimated annual burden of herpes zoster on Canadian healthcare

<table>
<thead>
<tr>
<th>Count</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>252,000</td>
<td>Physician consultations</td>
</tr>
<tr>
<td>130,000</td>
<td>New cases</td>
</tr>
<tr>
<td>2,000</td>
<td>Hospitalizations</td>
</tr>
<tr>
<td>17,000</td>
<td>PHN cases</td>
</tr>
<tr>
<td>20</td>
<td>Deaths</td>
</tr>
</tbody>
</table>

Lifetime risk as high as 30% of general population

Acute treatment of HZ

• Objectives – reduce viral replication, duration of rash and acute pain – does not significantly reduce incidence of PHN\(^1\)

• Treat preferably within 72 hours of rash onset in patients with any of the following criteria:\(^2\)
  – ≥ 50 years of age
  – Moderate or severe pain
  – Moderate or severe rash

• Treatment options\(^2\)
  – Acyclovir 800 mg oral 5 times daily or 10 mg/kg IV q8h for 7-10 days
  – Famciclovir 500 mg oral 3 times daily for 7 days
  – Valacyclovir 1,000 mg oral 3 times daily for 7 days

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Herpes zoster vaccine

Main criteria considered for recommendation of immunization program:¹

- Burden of illness of disease
- Vaccine efficacy and safety
- Cost-effectiveness of vaccination

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Vaccine efficacy vs. effectiveness

Efficacy
• Reduction of disease in vaccinated individuals relative to unvaccinated individuals under optimum conditions
• Double-blind, randomized, placebo-controlled clinical trials

Effectiveness
• Reduction in disease in vaccinated persons relative to unvaccinated persons under “real world” conditions
• Observational studies

Shingles prevention study design

- Double-blind, randomized, placebo-controlled clinical trial (efficacy)
  - 38,456 adults 60 years of age or older
  - Live-attenuated Oka/Merck VZV vaccine or placebo
  - Primary end point was burden of illness due to HZ
  - Secondary endpoint was incidence of PHN
  - 95% completed study, median 3.1 years

Shingles prevention study results

- Burden of illness reduced 61.1% (P<0.001)
- Incidence of HZ reduced by 51.3% (P<0.001)
- Incidence of PHN reduced by 66.5% (P<0.001)
- Significantly less zoster pain and discomfort than those who received placebo\(^1\)
- Reactions at injection site were more frequent among vaccine recipients but generally mild

Shingles prevention study results

HZ and PHN incidence

HZ incidence

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=642)</th>
<th>HZ vaccine (n=315)</th>
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</thead>
<tbody>
<tr>
<td>p</td>
<td>&lt;0.001</td>
<td></td>
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</table>

51% Reduction

PHN incidence

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=80)</th>
<th>HZ vaccine (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>p</td>
<td>&lt;0.001</td>
<td></td>
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</table>

67% Reduction

Shingles prevention study results

Burden of illness* according to age

<table>
<thead>
<tr>
<th>Efficacy (95% CI)</th>
<th>Placebo</th>
<th>Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>61.1% (51.1%-69.1%)</td>
<td>5.68</td>
<td>2.21</td>
</tr>
<tr>
<td>65.5% (51.5%-75.5%)</td>
<td>4.33</td>
<td>1.5</td>
</tr>
<tr>
<td>55.4% (39.9%-66.9%)</td>
<td>7.78</td>
<td>3.47</td>
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*Burden of illness: a composite measure of the incidence, severity and duration of pain and discomfort caused by HZ.

CI=confidence interval

Shingles prevention study results

**Effect of age on vaccine efficacy**

- **Reduction in incidence of HZ:**
  - 63.90%
  - 37.60%

- **Reduction in incidence of PHN:**
  - 66.80%
  - 65.70%

- **Reduction in incidence of HZ BOI score:**
  - 65.50%
  - 55.40%

*Herpes Zoster vaccine is indicated for the prevention of herpes zoster in individuals 50 years of age or older. It is not indicated to reduce the morbidity and complications associated with herpes zoster.

BOI = burden of illness

Shingles prevention study results
Vaccine safety

• Vaccine-related injection-site adverse reactions more common in the vaccine group than in the placebo group (48% vs. 17%)

• No difference in mortality (4.1% in each group)

• Similar rates of systemic adverse experiences (24.7% in the vaccine group vs. 23.6% in the placebo group)

Efficacy, safety, tolerability in persons aged 50-59 years

- 22,439 adults aged 50-59, mean follow-up of 1.3 years
- Vaccine efficacy = 69.8% (95% CI 54.1-80.6)
- Difference in adverse events primarily due to higher rates of injection-site AEs and headache

Duration of vaccine efficacy

• Short-Term Persistence Substudy\(^1\)
  – 7,320 vaccine and 6,950 placebo recipients followed through year 7
  – Statistically significant reductions for HZ burden of illness and incidence of HZ through year 5
  – Authors conclude that duration of zoster vaccine efficacy not known beyond 5 years – Long-Term Persistence Substudy analysis may provide additional data

Zoster vaccine cost effectiveness

- "A Systematic Review of the Cost Effectiveness of Herpes Zoster Vaccination"¹
  - 11 studies met criteria
  - All but one concluded vaccination to be cost effective
  - Highest sensitivity of cost effectiveness was age at vaccination, vaccine price and assumed duration of vaccine efficacy

Herpes zoster vaccine specifics

- Zostavax® (Live, Attenuated Virus Varicella-Zoster Vaccine)
  - Must be maintained at average temperature of -15°C or colder until reconstituted for injection

- Zostavax II® (Live, Attenuated Virus Varicella-Zoster Vaccine)
  - Refrigerator stable

Indication per product monograph: For prevention of herpes zoster (shingles). Indicated for immunization of individuals 50 years of age or older.

Herpes zoster vaccine contraindications

- Hx of hypersensitivity to any component of the vaccine, including gelatin
- Hx of anaphylactic/anaphylactoid reaction to neomycin
- Primary and acquired immunodeficiency states
- Immunosuppressive therapy (including high-dose corticosteroids)
- Active untreated tuberculosis
- Pregnancy

Persons 60 years old and older, no contraindications: 
Recommended, regardless of prior chickenpox history or varicella infection.

Persons aged 50 to 60 years, no contraindications: 
May be used – Evidence supports the use of herpes zoster vaccine in immunocompetent individuals ≥ 50 years

Answering patient questions

- Should I get the vaccine even if I don’t know whether I had chickenpox?
  - Yes, you should. It is estimated that 90% of Canadian adults have had the chickenpox infection.

- Can I get shingles from the vaccine?
  - There has never been a case of an individual getting shingles from the vaccine, although there is a small number of cases where people get a rash that resembles a shingles rash.

Answering patient questions

• If I get the vaccine, is it possible that I could infect a person in the house who has never had chickenpox?
  
  – There has never been a report of person-to-person transmission of the vaccine virus in the herpes zoster vaccine studies. Precautions are needed only in the unlikely event that a shingles-like rash develops in a person who has received the vaccine. These individuals should avoid close contact with people at risk of severe varicella.

• I have heard that people with chickenpox should not take ASA. Can I still take my daily ASA if I get the shingles vaccine?
  – The risk associated with taking ASA when chickenpox is present only applies to children. There are no worries with receiving the vaccine if you are taking ASA.

• If I have already been immunized with the chickenpox vaccine, should I receive the shingles vaccine?
  – No, it is not recommended that people who have already been vaccinated against chickenpox be vaccinated against shingles. This is because these people are not at risk of severe shingles.

I am over 80 years old and in relatively good health. Should I be vaccinated?
- Yes, in fact your age group is at greatest risk for shingles. The effectiveness of the vaccine appears to be the same as for other age groups.

This vaccine is expensive. Is it really worth the price?
- If you have ever seen anyone with a case of shingles you will know that it can be a very debilitating disease. The risk of postherpetic neuralgia increases with age and can cause excruciating pain and complications that may last a very long time. If you need time to consider, please ask your friends if they know someone who has had shingles, and ask about their symptoms before making a final decision.

Can the vaccine be given at the same time as other vaccines?

- The HZ vaccine can be administered at the same time as all other live and inactivated vaccines, including pneumococcal and influenza vaccines. This is based on Centers for Disease Control recommendations derived from a recent observational study that found no evidence of increased risk of HZ in the population receiving HZ vaccine and pneumococcal vaccine concomitantly.

Can the vaccine be administered when antiviral therapy is being taken?

- Patients who are taking acyclovir, famciclovir or valacyclovir should stop taking the medication for at least 24 hours before administration of the vaccine, and restart them at least 14 days after vaccination. This is because the antivirals could interfere with replication of the varicella zoster virus based vaccine. The NACI recommendations suggest individuals taking antivirals at the time of vaccination might benefit from a second dose of vaccine at least 42 days after the first dose and after discontinuation of therapy.

• Which patients are considered immunocompromised per the product monograph contraindications?
  
  – There is a grey area for patients who are mildly to moderately immunocompromised, where benefit to risk ratio is not known. This includes people taking immunosuppressive drug therapies or people with illnesses that alter the immune system (e.g., systemic lupus erythematosus). Therefore, the clinician must weigh individual circumstances. Extreme old age and presence of medical comorbidities such as diabetes and coronary artery disease are not contraindications.

• Should I be regularly recommending that my patients 50 years of age or older be immunized with herpes zoster vaccine?

  – Given that herpes zoster is associated with a high burden of illness and that the vaccine has been shown to be effective, safe, and cost-effective, the benefits of immunization as well as any concerns of patients should be discussed and documented for each member of this age group who do not have contraindications to receiving the vaccine. Individuals with chronic diseases such as diabetes and COPD are especially at risk for the comorbidities associated with this disease and should be approached.
The patient approach

“I want to let you know about the benefits of the shingles vaccine. Is that OK with you?”

“Have you heard about the new shingles vaccine?”

“Do you know anyone who has had shingles?”

“Are you aware that your risk for shingles starts to rise dramatically at age 50?”
The bottom line

- Herpes zoster is an often debilitating disease with a high prevalence of postherpetic neuralgia that is associated with significant burden of illness.
- Herpes zoster vaccine has been shown through large randomized placebo-controlled trials to significantly reduce incidence of HZ and PHN and burden of illness of disease.
- Herpes zoster vaccine is safe and cost-effective. There are few contraindications to its use. It may be given at the same time as other vaccines.
- Pharmacists are in an ideal position to raise awareness of the increasing risk with age and burden of illness associated with herpes zoster and to recommend herpes zoster vaccine to individuals age 50 years and older.
Questions?