Herpes Zoster Vaccine: Options for Consideration

Provincial Infectious Diseases Advisory Committee (PIDAC)

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This document was prepared by Drs. Anne Wormsbecker, Beate Sander and Shelley Deeks and approved by the Provincial Infectious Diseases Advisory Committee on Immunization (PIDAC-I). PIDAC-I is a multidisciplinary scientific advisory body who provide evidence-based advice to the Ontario Agency for Health Protection and Promotion (Public Health Ontario) regarding immunization. PIDAC-I's work is guided by the best available evidence and updated as required.

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Table of Contents

Appendices:

Tables:

Figures:

Background

After primary infection, varicella zoster virus (VZV) establishes dormancy in the dorsal root ganglia of spinal nerves, as well as in cranial nerve roots. It remains latent for years but can reactivate, causing a painful rash in a dermatomal distribution called herpes zoster (HZ) or shingles. The risk of reactivation increases with age.

Reactivation of VZV along the sensory distribution of the of the ophthalmic division of the trigeminal nerve can cause herpes zoster ophthalmicus (HZO), which may threaten vision due to keratitis or chorioretinits of the eye.[1] The most common complication of HZ is post-herpetic neuralgia (PHN) which occurs in about 20% of people.[2] PHN is a chronic pain condition that impacts affected individuals, the health care system, and society-at-large.[2,3,4] There are a number of other, less common complications, including disseminated HZ, that occur primarily in patients who are immunocompromised.[1] An HZ vaccine (Zostavax®, Merck) was developed to prevent HZ and PHN and was approved for use in Canada in 2008.[5]

During meetings on August 15, 2012, November 12, 2012, and January 16, 2013, Ontario's Provincial Infectious Diseases Advisory Committee on Immunization (PIDAC-I) discussed the characteristics of the presently-available HZ vaccine; the epidemiology and burden of HZ in Ontario, Canada; the health economics of HZ vaccine; and current Canadian and American recommendations. This document summarizes the information reviewed at those meetings and provides evidence-based scientific and technical advice from PIDAC-I regarding options for consideration with respect to the use of HZ vaccine in Ontario.

Herpes Zoster Vaccines

Zostavax® is a live-attenuated vaccine containing a high concentration of the Oka/Merck strain of VZV. Each 0.65mL single-dose vial contains a minimum of 19 400 plaque forming units of the virus, about 14 times more than the varicella vaccine given to children.[5]

Zostavax® was initially approved for use among persons 60 years and older by the Biologics and Genetic Therapies Directorate (BGTD) of Health Canada in August 2008.[5] and in May 2011 it was approved for use in those age 50 years and older.[6] This vaccine must be stored frozen at minus 15 degrees Celsius and is reconstituted with 0.7mL of sterile water diluent prior to administration via subcutaneous injection. Maintenance of frozen cold-chain is crucial and the vaccine needs to be used within 30 minutes of reconstitution.

A refrigerator-stable version of HZ vaccine, Zostavax II®(Merck), received a Notice of Compliance from BGTD in October 2011.[7] However, according to the manufacturer, this product will not be available in Canada until approximately 2015 (personal communication, C. Paquette, Merck, 10 May 2012).

Herpes Zoster Vaccine Efficacy and Safety

The efficacy of Zostavax® was established in an American multi-centre double-blind randomized placebo-controlled study known as the Shingles Prevention Study (SPS).[8] The study looked at the effect of HZ vaccine on the incidence of both HZ and PHN, as well as the burden of illness caused by HZ in 38 546 healthy adults aged 60 years and over. Those with a past history of HZ were excluded. The participants were followed for a median of 3.1 years and Zostavax® was most efficacious in younger members of the study population. For the prevention of HZ, vaccine efficacy was 63.9% (95% CI: 55.5, 79.9%) in 60-69 year olds whereas it was only 37.6% (95% CI: 25.0, 48.1%) efficacious in those ≥ 70 years old. When the analysis was restricted to those ≥ 80 years old, efficacy was 18% (95% CI: -29, 48%). Regarding PHN (defined as pain lasting more than 90 days after the onset of HZ rash), efficacy was 65.7% (95% CI: 20.4, 86.7%) in 60-69 year olds; 66.8% (95% CI: 43.3, 81.3%) in ≥ 70 years old; and 39% (95% CI: 7, 59%) in ≥ 80 year olds.[1,8]

In the SPS, burden of illness was defined as severity of illness (response on "worst pain" question of validated Zoster Brief pain inventory [ZBPI]) plotted against time for 182 days following onset of HZ rash. The mean burden of illness score was significantly lower in the Zostavax® group versus the placebo group and reductions in severity of illness were greater in older persons, supporting that Zostavax® reduces an individual's burden of illness due to shingles.[8]

In April 2012, Schmader and co-authors published a study of HZ vaccine efficacy in persons 50-59 years of age. There were 22 439 participants across North America and Europe but the duration of follow-up was short (mean 1.3 years, range 0 days to 2 years). The authors did not examine the efficacy of Zostavax® against PHN, a condition less likely to occur in this age group, but found a vaccine efficacy of 69.8% (95% CI: 54.1, 80.6) for the prevention of HZ.[9]

Vaccine safety was studied in an adverse event sub-study of the SPS, in which 19 000 people were given Zostavax® and an equal number were given placebo and observed for the occurrence of adverse events for 42 days after vaccination, there was no difference in rates of death or serious adverse events between groups.8 Half of the Zostavax® recipients had one or more signs of injection site reaction, but fever after vaccination was very rare (< 1%). Fifty-five people (0.3% of vaccines) developed a rash characteristic of chickenpox or shingles. However, there was no evidence of transmission of the vaccine strain.[1,8]

Epidemiology and Burden of Zoster

Based on published data using health-care administrative databases, Tanuseputro and co-authors reported that the crude annual rate of HZ in Ontario between April 1992 and March 2010 was 3.2/1000 population.[10] Incidence increased with age, particularly among persons 70 years of age and older (see Table 1). Hospitalizations and outpatient visits declined over the time period but overall age-standardized incidence did not change.

TABLE 1. HERPES ZOSTER-RELATED EVENTS IN ONTARIO BY AGE GROUP, FISCAL YEARS 1992-2009

	Annualized rate of zoster-related events over study period (per 100 000)		
	Hospitalizations (per 100 000)	Outpatient visits (per 100 000)	Incidence rate (per 100 000)
Overall	6.7	527	323
Sex			
Males	5.2	412	256
Females	7.4	568	245
Age Group (years)			
0-9	1.7	150	128
10-19	1.5	190	154
20-39	1.1	293	215
40-49	2.1	409	276
50-59	4.6	730	455
60-69	11.9	1157	644
70-79	57.3	1686	826
80+	75.0	1783	841

Source: Tanuseputro P, Zagorski B, Chan KJ, Kwong JC. Population-based incidence of herpes zoster after introduction of a publicly funded varicella vaccination program. Vaccine. 2011;29(47):8580-4.

This study encompassed a time period that included no childhood immunization against varicella (1992-2001), privately available varicella vaccine (2001-2005), and a publicly-funded childhood varicella vaccination program (2005-2010). Although the post-varicella vaccination program period was relatively short, especially considering that HZ is predominantly a disease of adults, the authors did not observe an increase in medically-attended HZ episodes after the introduction of the varicella vaccination program. There is conflicting data regarding the short-term effect of childhood varicella immunization programs on the epidemiology of HZ. It is thought that exposure to the varicella virus among persons who have been previously infected serves as a 'natural booster' and protects against reactivation of the virus.[11] In the setting of relatively recent introduction of childhood varicella immunization programs, the population includes those who had wild-type infection, as well as those who were vaccinated, yet there is decreasing circulation of the wild-type virus in the population. Children and adults who previously had varicella infection and have varicella zoster virus dormant in their nervous systems are therefore exposed less frequently to 'natural boosters' and it has been suggested that they may be more likely to develop HZ. As stated above, Tanuseputro and co-authors did not observe this in Ontario nor was it seen in the United States (US) between 1993 and 2006.[12] Controversial data from the Antelope Valley Varicella Active Surveillance Project (AV-VASP), focusing on persons less than 60 years of age, suggests an increase in HZ incidence among persons who had acquired natural VZV infection, since the licensure of varicella vaccine.[13]

The epidemiology of HZ has also been studied in a number of other Canadian provinces. In British Columbia, between 1994 and 2003, there were five deaths per million persons among those ≥ 65 years of age.[14] In Alberta, annualized incidence from 1986 to 2002 was >10/1000 population for persons 75-years of age and older,[15] not too dissimilar to Ontario's incidence among persons 80-yearof age and older (8.4/1000 persons, see Table 1 above). As in Ontario, a Manitoba study found that risk of

hospitalization was greater with increasing age. For example, in their analysis of 18 years (1979-1997) of health care administrative data, Brisson and co-authors found that 2.8% of 45 to 64-year-old cases were hospitalized, whereas 10.6% of persons 65-years of age and older were hospitalized.[16]

Beyond population-based epidemiology, the individual and system-level burdens of HZ are important considerations. Regarding individual burden of illness, the ZBPI was designed to specifically assess HZ-related pain. It was adapted from the Brief Pain Inventory (BPI) to include factors specific to HZ such as itch and the ZBPI is considered to have good reliability and validity.[4] A group of Canadian researchers prospectively enrolled patients with HZ and assessed health-related quality of life using the ZBPI and a general measure of health-related quality of life, the EuroQuol 5-D (EQ-5D). Among 261 cases of HZ, recruited from the offices of 83 physicians across Canada who had attended a pharmaceutical-sponsored training session (mean age 65.4 years [standard deviation 10.8 years]), the median duration of pain was 32.5 days. The proportion who experienced PHN (≥90 days of pain after rash onset) was 24% (n=63). In the PHN group, 65% continued to report problems in the pain and discomfort domain of the EQ-5D 180 days after the onset of the HZ rash. About 35% were experiencing limitations in mobility at this stage and approximately 45% had problems in the EQ-5D anxiety/depression domain. This study reveals that HZ, and PHN specifically, reduces health-related quality of life.[4]

Economic Evaluations

A limited review of the cost-effectiveness of HZ vaccination (Zostavax) in adults was conducted on May 28, 2012.

Literature search

A literature search was performed to identify published literature on the cost-effectiveness of HZ vaccination in adults. Embase, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) were searched using search terms related to the disease, the vaccine and economic evaluation. All terms are listed in Appendix 1.

After removing duplicates and limiting by publication date (2000-Current), language (English), human, and adults 18 years and older, 58 references were obtained. A first screening excluded articles that did not report an original, comparative economic evaluation in a Western Country. Subsequently, 13 articles were retrieved in full text (see appendix 2 for flow chart). One further article evaluating the cost-effectiveness of a combined varicella and HZ vaccination program was excluded. The remaining 11 articles are included in this synthesis.

Assessment of cost-effectiveness

Threshold values based on the cost per outcome gained are often used to determine whether an intervention is considered cost-effective. Since the 1990's, a threshold of $50,000 per quality-adjusted life-year (QALY) gained has been widely used to classify interventions as cost-effective in the US and many other jurisdictions, including Canada.[17] A threshold of £30,000 per QALY gained is commonly used in the United Kingdom (UK)[18] and in Canada, a range rather than a single cut-off has been suggested, where interventions costing <20,000 Canadian dollar are considered highly cost-effective and those between

$20,000 and $100,000 per QALY cost-effective.[19] Finally, the World Health Organization's Choosing Interventions that are Cost-Effective Collaboration (WHO-CHOICE) suggests threshold values based on gross-domestic product (GDP) to categorize the relative cost-effectiveness of interventions: an intervention is considered highly cost-effective when it is less than GDP per capita per Disability-Adjusted Life Year (DALY) averted; an intervention is cost-effective when it is between one and three times GDP per capita per DALY averted; and an intervention is not cost-effective when it is more than three times GDP per capita per DALY averted.[20]

This review assesses cost-effectiveness of intervention across a variety of countries. To ensure consistency across countries, the threshold values suggested by WHO-CHOICE were chosen for this report, recognizing that DALYs and QALYs are different measures of health-adjusted life years. However, the threshold of 'less than GDP per capita per DALY averted' is consistent with commonly used thresholds using QALY as effectiveness measure. The GDP per capita is approximately $40,000 in Canada. Therefore interventions with an incremental cost-effectiveness ratio (ICER) of less than $40,000 per QALY would be considered highly cost-effective, interventions with an ICER between $40,000 and $120,000 per QALY gained would be considered cost-effective in Canada.

It is also noted that a threshold of three times GDP per capita is high and therefore interventions at this level may be considered unaffordable. One times GDP per capita is a more desirable threshold. Given the arbitrary nature of the thresholds used commonly today, they remain controversial and should be used only for general guidance. Constant GDP for each country in the year of costing was obtained from the World Economic Outlook Database compiled by the International Monetary Fund.[20]

Interventions were also described as dominant and dominated, as necessary. A dominant intervention is less costly and more effective than a comparator, whereas a dominated intervention is more costly, yet less effective than a comparator.[21]

Characteristics of included studies

Studies included in this review are from the following jurisdictions: Canada (n=2), the US (n=3), the UK (n=2), Belgium (n=2), the Netherlands (n=1) and Switzerland (n=1). All economic evaluations are model-based cost-utility analyses, estimating cost per QALY gained. The models predict lifetime health outcomes and costs for cohorts aged 50 years and older. Typically, health outcomes are defined as HZ (mild, moderate, severe) and PHN. All studies use vaccine efficacy data from the SPS8 and most studies also use other data from the SPS to parameterize the model (e.g. risk and severity of HZ and PHN). Most evaluations are performed from the health care payer perspective (including all industry-sponsored studies), some from the society perspective and some report both. Only one HZ vaccine (Zostavax®) was evaluated in the studies. Health outcomes and costs are discounted according to national guidelines. Five out of 11 studies were funded by the sole manufacturer of the vaccine (Merck).[22-26]

Findings

Overview

Appendix 3 provides a detailed overview of methods and results.

Methods across the included studies are consistent, however, some of the assumptions (vaccine efficacy endpoints, PHN severity, duration of protection, vaccine cost) vary substantially. Despite this variability, studies reporting the cost-effectiveness from the health care perspective conclude that HZ vaccination is cost-effective (2 of 8 studies)[22,23] or even highly cost-effective (6 of 8).[22-26] One further study (Bilcke 2012, described below) found HZ vaccination to be highly cost-effective under favorable assumptions only.[22] All studies reporting the cost-effectiveness from the societal perspective conclude that HZ vaccination is cost-effective (3 of 3 studies),[24-26] but only 1 study found it to be highly cost-effective.[32] Importantly, none of the studies included costs for maintaining the cold-chain, required for a frozen product. Results are most sensitive to:

1. Age at vaccination,

2. Vaccine-related parameters [vaccine efficacy (HZ incidence only or HZ disease burden including PHN), duration of protection, and vaccine cost],

3. HZ/PHN disease burden (pain distribution, disease severity [QALYs], cost and duration of PHN). Most of the benefit of vaccination can be attributed to reducing the burden of PHN.

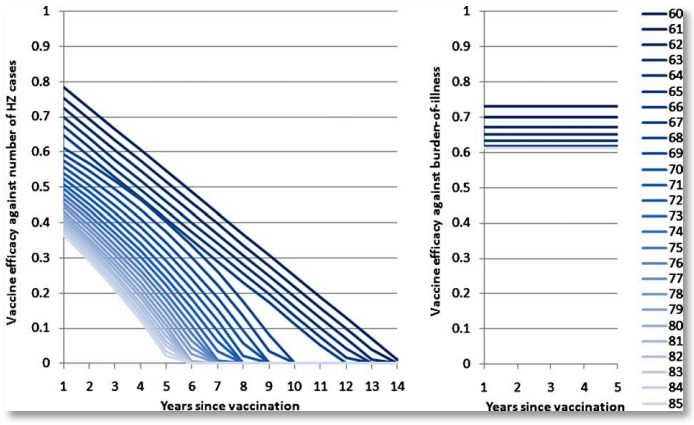
Because of limited evidence available (e.g. only a single study measured the efficacy of Zostavax in preventing HZ), uncertainty remains related to vaccine efficacy and to burden of illness. The analyst therefore has to make assumptions which in turn affect the results as illustrated in the analysis by Bilcke 2012 for Belgium.[22] Bilcke present two scenarios: one where the analyst's assumptions are most in favor of vaccination and one where they are least in favor of vaccination. The scenarios are described in Table 2 and Figure 1 below.

TABLE 2: UNCERTAINTIES AND THE ASSUMPTIONS MOST AND LEAST IN FAVOR OF VACCINATION AGAINST HERPES ZOSTER FOR EACH OF THESE UNCERTAINTIES (BILCKE 2012)[22]

Uncertainties	Assumption most in favor of vaccination	Assumption least in favor of vaccination
Population that can benefit from the vaccine	Everybody age 60 to 85 years old	According to inclusion criteria of the Shingles Prevention Study (excluded immune compromised persons, persons with HZ in the past, and persons with other conditions, e.g. diabetes)[6]
Mortality rate	Highest estimate (depending on age; 0.06 to 0.63 per 100,000)	No deaths
Severity-of-illness (SOI) score ambulatory HZ episode	Based on Drolet3[3] data (higher SOI scores)	Based on Scott2[2] data (lower SOI scores)
Endpoint for vaccine efficacy	Burden of illness (duration and severity) due to HZ, including PHN	Number of HZ cases
Vaccine efficacy by age at vaccination and time since vaccination	Vaccine efficacy does not differ significantly between age groups, no waning (see Figure)	Vaccine efficacy differs significantly between age groups, waning (see Figure)

Source: Bilcke J, Marais C, Ogunjimi B, Willem L, Hens N, Beutels P. Cost-effectiveness of vaccination against herpes zoster in adults aged over 60 years in Belgium. Vaccine 2012; 3:675-684.

FIGURE 1. ESTIMATED VACCINE EFFICACY OVER TIME (X-AXIS) AND BY AGE AT VACCINATION (DIFFERENT LINES) USED AS INPUT FOR THE SCENARIO LEAST IN FAVOUR OF VACCINATION (LEFT PANEL) AND THE SCENARIO MOST IN FAVOUR OF VACCINATION (RIGHT PANEL)



Source: Bilcke J, Marais C, Ogunjimi B, Willem L, Hens N, Beutels P. Cost-effectiveness of vaccination against herpes zoster in adults aged over 60 years in Belgium. Vaccine 2012; 3:675-684.

In the scenario where assumptions are most in favor of vaccination, HZ vaccination was found to be highly cost-effective for all age groups (60-85 years at time of vaccination) whereas under the least favorable assumptions, it was found not to be cost-effective, except for 60 year olds and 70 year olds (Table 3 below).[22]

TABLE 3. COST-EFFECTIVENESS RESULTS FOR CHOICES MOST AND LEAST IN FAVOR OF VACCINATION

	Choices most in favor of vaccination			Choices least in favor of vaccination		
Age	Cost (€) per QALY	Highly cost-effective	Cost-effective	Cost (€) per QALY	Highly cost-effective*	Cost-effective*
60 y	1,251	Yes	Yes	48,978	No	Yes
70 y	2,294	Yes	Yes	73,513	No	Yes
80 y	3,988	Yes	Yes	132,220	No	No
85 y	5,498	Yes	Yes	303,705	No	No

Source: Bilcke J, Marais C, Ogunjimi B, Willem L, Hens N, Beutels P. Cost-effectiveness of vaccination against herpes zoster in adults aged over 60 years in Belgium. Vaccine 2012; 3:675-684.

* Highly cost-effective, less than 1 times GDP/capita per QALY gained; cost-effective, 1 to 3 times GDP/capita per QALY gained

Most economic evaluations found HZ vaccination to be most cost-effective in adults 65-70 years of age. This reflects the tradeoff between vaccine efficacy (greater in younger age groups) and potentially limited duration of protection on the one hand and disease burden of HZ and PHN (greatest around 70 years of age) on the other. Only three (industry-sponsored) studies considered younger age groups (50-59 years old).[18-20] Two found vaccinating 50 year olds to be highly cost-effective[22-24] and one found it to be cost-effective.[22]

Overall, reported results were generally more favorable in industry-sponsored studies (5 of 5 report vaccination to be highly cost-effective) [22-26] than in independent studies (3 of 6 report vaccination to be highly cost-effective,[27,29,32] though one of these only under assumptions most in favor of the vaccine).[27] However, all independent studies report vaccination to be cost-effective, [26-31] though one of these in females only.[31]

If vaccinating a prevalent cohort, cost-effectiveness estimates may improve over time, as the cost-effectiveness converges to that of the youngest group. This is because vaccinating older age groups is less cost-effective than vaccinating younger age groups. Cost effectiveness could also improve if the burden of disease increases.

Canadian studies

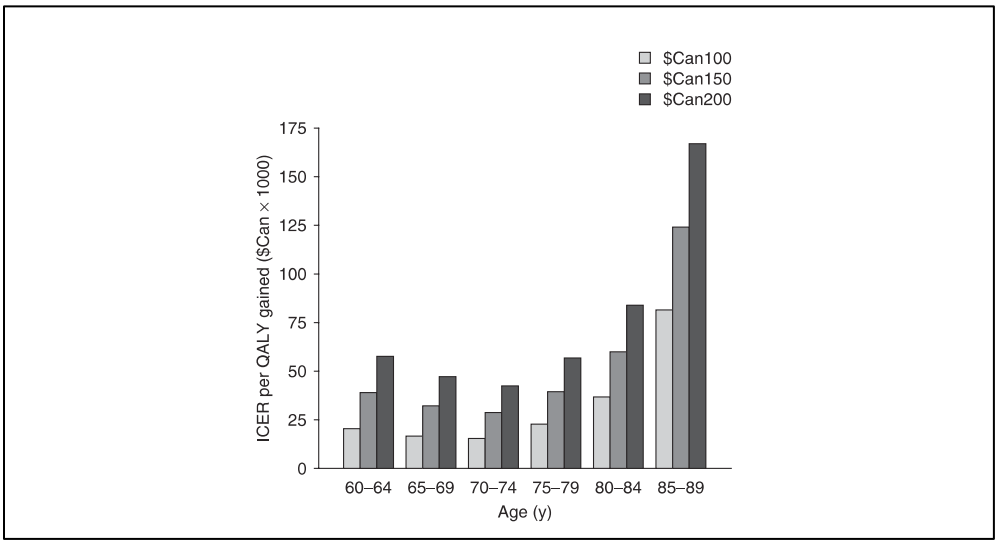
The review identified two studies from Canada, one independent study (Najafzaedh 2009[23]) and one industry-funded (Brisson 2008[23]). Both studies are very similar: both are from the health care payer perspective, use a similar model structure and are primarily based on the SPS. Both assume a vaccine price of $150 (Canadian dollars) in the base case analysis, which is close to the current pharmacy price of Zostavax ($156 + $3.89 dispensing fee). Vaccine-related costs (maintenance of cold-chain with a frozen product, vaccine administration) were not considered in either study. Costs and QALYs are discounted at 5% per annum consistent with Canadian guidelines. The studies differ in the target population and assumptions about waning rate. Najafzadeh assesses immunizing a prevalent cohort aged 60 years and older (i.e. all individuals 60+ years) and assumes a non-zero waning rate in the base case (half-life of 15 years or equivalently, a 4.3% annual waning rate).[23] Brisson assesses immunizing an incident cohort aged 65 years (i.e. 65 year olds only) and assumes a zero waning rate in the base case (i.e., no waning immunity).

Najafzadeh reports an ICER of $41,709 per QALY gained, with a proportion of 52% of simulations resulting in the immunization program being cost-effective at a threshold $50,000 per QALY gained (71% at $100,000 per QALY gained). Results are also presented by age group (Figure 2), showing immunization to be most cost-effective in 70 to 74-year-olds.[23]

Brisson reports an ICER of $33,152 per QALY gained, with 70% of simulations resulting in the immunization program being cost-effective at a threshold $40,000 per QALY gained (90% at $50,000 per QALY gained). Brisson also presents results by age group vaccinated and shows immunization to be most cost-effective in 70 year olds ($31,662/QALY), and the least cost-effective in 50 year olds ($50,644/QALY). [23]

Both analyses are sensitive to age at vaccination, vaccine cost, waning rate, and PHN burden of illness.

FIGURE 2. EFFECT OF AGE AND VACCINE COST ON THE INCREMENTAL COST-EFFECTIVENESS RATIO



Source: Najafzadeh M, Marra CA, Galanis E, Patrick DM. Cost effectiveness of herpes zoster vaccine in Canada. Pharmacoeconomics 2009; 12:991-1004.

Conclusion of Economic Evaluation Review

HZ vaccination appears to be cost-effective from a health care payer perspective under a wide range of assumptions, particularly for adults 65-70 years of age. The cost-effectiveness of HZ vaccination varies depending on age at vaccination, vaccine effectiveness (HZ, PHN), duration of protection, HZ/PHN disease burden and vaccine cost.

Herpes Zoster Vaccine Policy and Programs

PIDAC-I reviewed American and Canadian HZ vaccine policy and programs. The vaccine was approved by the American Food and Drug Administration (FDA) in May of 2006 for use in persons aged 60 years or older.[1] In October of 2006, the American Advisory Committee on Immunization Practices (ACIP), which in contrast to the Canadian National Advisory Committee on Immunization (NACI) considers economics analyses as part of their decision-making process, recommended a single dose of HZ vaccine in this age group.[1] The ACIP recommendations provide detailed information on the use of this live vaccine in persons with a history of HZ (recommended), receiving blood products (no contraindications or time delay required), as well as for persons with anticipated immunosuppression (administer 14 days prior to immune suppression), receiving anti-viral medications (discontinue 24 hours prior to and 14 days after HZ vaccine), and with immunodeficiency or requiring chronic immune suppression (generally not recommended but permissive with some low-dose immunosuppressive agents).[1] More recently, the FDA approved Zostavax® for use in 50-59 year olds[25] however the ACIP declined to recommend the vaccine for this age group, noting there are "limited data on long-term protection" and a shortage of the vaccine at the time;[33] the latter issue has since been resolved. Zostavax® is funded in the US for some Medicare (national social insurance program for Americans aged 65 years and over) recipients.[26]

From a Canadian perspective, as noted previously, Zostavax® was approved for use in Canada in 2008 for persons 60 years and older.[5] Like the FDA, Health Canada has since approved the product for administration to 50-59 year olds.[6] Canada's NACI recommends Zostavax® for the prevention of HZ and its complications in persons 60 years or older without contraindications[3] and NACI states that the vaccine *may* be used in individuals 50-59 years of age. Due to insufficient evidence, NACI does not provide a recommendation for use of the vaccines in persons with a past history of HZ, and gives much more general information on vaccinated people with immune compromising conditions than the ACIP. At present there are no publicly-funded HZ vaccine programs in any province or territory in Canada. Canadians who are eligible for HZ vaccine may purchase Zostavax® privately and private insurance plans may offer reimbursement. Based on an online environmental scan, Zostavax® is not included in the formularies of provincial/territorial drug benefit programs, including the Ontario Drug Benefit (ODB) for those who have reached 65 years of age (www.drugcoverage.ca, accessed 2 November 2012).

Additional Programmatic Considerations

Simultaneous Administration with Other Adult Vaccines

In Ontario, all adults are eligible to receive publicly-funded annual influenza vaccine, and boosters of tetanus-diphtheria (Td) vaccine every 10 year. In addition, 19-64 year-olds are eligible for a single lifetime dose of tetanus-diphtheria-acellular pertussis (Tdap) vaccine and all adults 65 years of age and older are eligible for pneumococcal polysaccharide vaccine. When an adult presents to a health care provider for immunization, there is an opportunity to give multiple injections. As such, the *Canadian Immunization Guide* supports multiple vaccine injections at a single visit[27] and NACI recommends that Zostavax® can be given concurrently with influenza and pneumococcal polysaccharide vaccine.[28]

NACI's recommendations regarding influenza are based on a double-blind randomized-controlled trials conducted by Merck.[29,30] There were no statistically significant safety nor immunogenicity concerns when Zostavax® and seasonal influenza vaccine were concomitantly given to a group of people 50 years and older.[36]

In a study by McIntyre and co-authors, antibody responses to HZ vaccine were lower in the group who received it concurrently with pneumococcal polysaccharide vaccine compared to those who received the two vaccines separated by an interval of 4 weeks. Redness at the injection site was also significantly greater in the concomitant group.[30] Based on this data, Merck's product monograph recommends against simultaneous administration of Zostavax® and pneumococcal polysaccharide vaccine.

However, more recently, Tseng and co-authors published observational data from a large California health-maintenance organization analyzing the issue of simultaneous administration of HZ and pneumococcal polysaccharide vaccines. Between January 2007 and June 2010, 7187 people received Zostavax® and pneumococcal polysaccharide vaccine at the same time and 7179 were given the two on separate occasions. In the retrospective analysis, controlling for age, sex, race, number of medical visits in the year prior to follow-up and chronic conditions, there was no difference in the risk of HZ in the two groups.[31] The authors concluded that in a real-world setting, there is no reduced effectiveness of Zostavax® when it is given along with pneumococcal polysaccharide vaccine. However, the possibility of residual confounding remains and there is likely a healthy participant bias, as concomitant vaccine recipients were younger and had fewer chronic medical conditions.

Although, a search of the literature and the clinical trials registry (clinicaltrials.gov) did not reveal any studies of simultaneous administration of HZ vaccine and Tdap, it is important to note the benefit of giving vaccines concomitantly and not risking a lost opportunity to give a vaccine to someone who may not return for follow up.

Feasibility Issues

The members of PIDAC-I discussed the pragmatics of the use of a vaccine that requires frozen storage. Currently there are no publicly-funded vaccines in Ontario with this temperature requirement. Keeping the vaccine frozen would mean that the manufacturer, Ontario Government Pharmacy, local public health

units, and health care practitioners or pharmacies would require adequate freezer facilities to maintain cold chain. Cold chain would also need to be maintained during transport. This may require the purchase of a new freezer or refrigerator/freezer unit as the vaccine must be kept in a freezer at minus 15 degrees Celsius with a separate door. Therefore, a "bar fridge" style unit with a small area for frozen items but a single door is not adequate. Because the vaccine must be used within 30 minutes of reconstitution, the delivery of numerous HZ vaccines in residential settings, such as long-term care facilities, would be logistically difficult as vaccine cannot be reconstituted far in advance of use. The presently available frozen product poses a number of vaccine-delivery challenges, which is unfortunate given that Zostavax®II, Merck's refrigerator-stable vaccine, will not be available until 2015 (according to the manufacturer).

Duration of Protection

Over 14 000 participants in the SPS took part in the Short-Term Persistence Sub-Study.[32] The incidence of HZ and PHN was observed in these individuals during a two-year period from five years to seven years after having received the vaccine. The mean age at enrollment in this sub-study was 70.3 years and 7320 of the 14 270 participants were vaccinated. A comparison of vaccine efficacy (VE) between the initial SPS and the persistence study is shown in Table 4. [1,32]

TABLE 4. HERPES ZOSTER VACCINE EFFICACY IN SHINGLES PREVENTION STUDY AND SHORT-TERM PERSISTENCE SUB-STUDY

Study	Years post-vaccination	VE for HZ burden of illness	VE for incidence of HZ	VE for incidence of PHN
		Point Estimate % (95% CI)		
Shingles Prevention Study (n=38 546)	0 to 4.9	61.1 (51.1, 69.1)	51.3 (44.2, 57.6)	66.5 (47.5, 79.2)
Short Term Persistence Substudy (n=14 270)	3.3 to 7.8	50.1 (14.1, 71.0)	39.6 (18.2, 55.5)	60.1 (-9.8, 86.7)

The point estimate of VE was lower against HZ burden of illness, HZ incidence and incidence of PHN among those who were observed from 3.3 to 7.8 years after vaccination compared to those who were observed for up to five years in the original study, suggesting waning immunity over time. For incident HZ, VE ranged from 40-50% in years two to five post-vaccination, dropping to 30% in the sixth year after HZ vaccination (with non-significant lower limit of confidence interval). In the seventh year post-immunization, only 3139 participants (among more than 35 000 original SPS participants) were studied. VE was more than 50% however the confidence interval was very wide and non-significant.[32]

Although there was attrition during the periods of observation for both studies, this is the most current data regarding the duration of protection offered by Zostavax®. It appears that the vaccine is efficacious up to four years after vaccination but efficacy beyond this point is uncertain. It should also be noted that the duration of protection may vary with age of vaccination, given the findings from the clinical trials regarding vaccine efficacy and age (i.e., the oldest adults have lower VE). There may be a role for booster doses and trials of both the long-term efficacy of Zostavax® as well as the need and response to booster doses are under way.[33]

Summary

In summary, HZ is a relatively common condition which can be a debilitating, primarily due to the pain and disability associated with PHN. A safe, live-attenuated vaccine to protect against HZ and PHN is approved for use in Canada and recommended by NACI for use in persons 60 years of age and older. The vaccine, which can reasonably be administered simultaneously with other adult immunizations, offers protection for a minimum of four years. Further, economic evidence indicates that HZ vaccination is likely cost-effective from a health care payer perspective under a wide range of assumptions, particularly for adults 65-70 years of age. However, at present a refrigerator-stable version of Zostavax® is authorized for sale in Canada but will not be available until 2015, according to the manufacturer. The delivery of a vaccine that requires frozen storage presents a number of logistical challenges in the maintenance of cold chain.

Options for Consideration

PIDAC-I is providing the following options for consideration regarding a publicly funded program for Zostavax®:

1. In light of NACI recommendations in favour of HZ vaccine, the significant burden of illness from HZ in older adults, as well as economic analyses indicating that it is cost effective from the health care payer perspective, particularly among persons 65 to 70 years of age, but also in other age groups for whom the vaccine is recommended, a publicly funded HZ vaccine program should be considered. Such a program targeting older adults has the potential to reduce the burdens of HZ for both individuals and the health care system. There are three main options for a publicly funded HZ vaccine program that the Government of Ontario could consider:

    a) A publicly funded HZ vaccination program for persons 65 years of age, with eligibility in perpetuity. A program such as this would be relatively inexpensive and is anticipated to be cost-effective, based on the economic literature reviewed. Importantly, it would be programmatically convenient as 65-year-old adults are also eligible for pneumococcal polysaccharide vaccine.

    b) A publicly funded HZ vaccination program for all persons 60 to 70 years of age. Initiation of this program option would be more expensive than option one because more individuals would be eligible at the outset of the program. However, the delivery of HZ vaccine to persons in this age group was also cost-effective, according to the economic models reviewed and especially under favourable model assumptions. This option would provide an opportunity to vaccinate more individuals at risk of HZ and post-herpetic neuralgia, given the increased risk of both with increasing age.

    c) A publicly funded HZ vaccination program for all persons 60 years and older. This would be consistent with NACI recommendations While this would be the most expensive option to initiate due to the large eligible group and may not be cost-effective for persons > 80 years, when all age groups were combined in economic analyses, HZ vaccine was still shown to be cost-effective under favourable model assumptions. This option is also the most equitable, as all persons for whom the vaccine is recommended by NACI would be eligible.

Currently, only a freezer stable HZ vaccine is on the market. Given the programmatic issues and potential wastage that this may entail, the government of Ontario may choose to defer a publicly-funded HZ program until a refrigerator-stable product becomes available.

2. If Ontario chooses not to offer a publicly funded HZ vaccination program, the vaccine remains available to Ontarians who chose to pay for it (i.e., status quo). However, the potential to reduce the burden of HZ in Ontario through privately available HZ vaccine is unknown and would be substantially lower than through a publicly-funded program. This option, however, also has a cost to the province, due to the utilization of the health system by those who are affected by HZ. On a societal basis, this also would result in continued inequitable access to the vaccine, as only people who are able to purchase the product would benefit.

Other areas of consideration suggested by PIDAC-I regarding HZ prevention include**:**

Advocacy

Although Zostavax® is licensed for persons 50 to 59 years of age, there is currently no definitive recommendation for its use in this age group. Public Health Ontario should encourage NACI to make a definitive recommendation for this group in whom HZ vaccine is immunogenic, but who have a lower burden of illness.

Surveillance

To assess the impact of both varicella and HZ vaccines in Ontario, surveillance for both varicella and HZ disease should be improved by PHO. This would be valuable in that it would enable the province to evaluate the impact of both varicella and HZ vaccines. Options for surveillance include use of both reportable disease and administrative data.

Research

Public Health Ontario should be encouraged to continue to monitor research on the duration of protection offered by Zostavax® as it is currently not known whether one or more booster doses will be needed. This process will allow further review concerning booster doses as new information becomes available.

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Appendix 1: Search Terms for Review of Economic Evaluations

Disease

Herpes zoster.mp. or exp Herpes Zoster

Vaccine

Zostavax.mp. or exp Herpes Zoster Vaccine

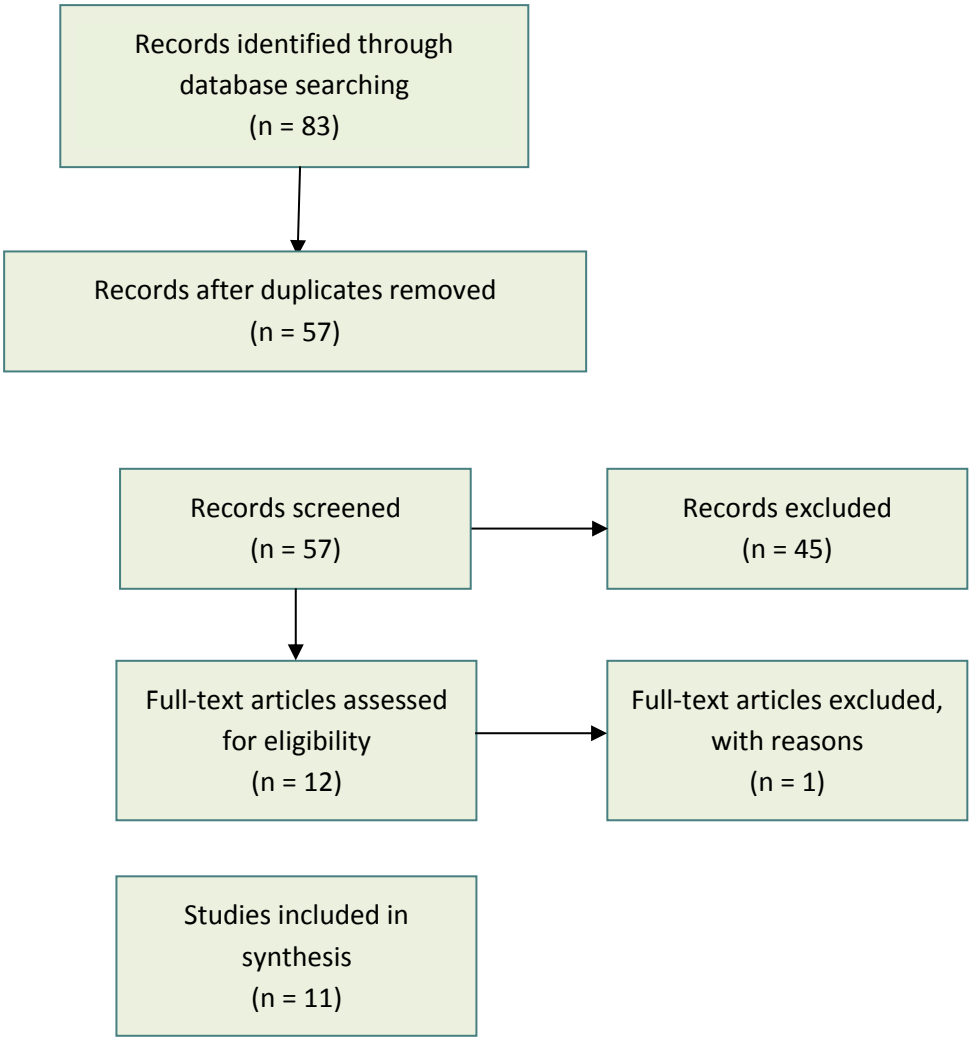
Economics - Medline

Economics/ or Resource Allocation/ or Health Care Rationing/ or "Costs and Cost Analysis"/ or Cost Allocation/ or "Cost-Benefit Analysis"/ or Cost Control/ or Cost Savings/ or "Cost of Illness"/ or Health Care Costs/ or Direct Service Costs/ or Drug Costs/ or Employer Health Costs/ or Hospital Costs/ or Health Expenditures/ or Capital Expenditures/ or "Economics, Behavioral"/ or "Economics, Hospital"/ or Hospital Charges/ or Hospital Costs/ or exp "Economics, Medical"/ or "Economics, Nursing"/ or "Economics, Pharmaceutical"/ or "Fees and Charges"/ or "Fees, Medical"/ or "Fees, Pharmaceutical"/ or Prescription Fees/ or Hospital Charges/ or Prescription Fees/ or "Financing, Organized"/ or exp "Financing, Government"/ or Health Care Sector/ or Investments/ or exp Taxes/ or exp Models, Economic/ or exp Obesity/ec or Overweight/ec or (cost adj1 effectiv$).mp.

Economics – Embase

behavioral economics/ or cost benefit analysis/ or cost control/ or cost effectiveness analysis/ or cost minimization analysis/ or "cost of illness"/ or cost utility analysis/ or cost/ or drug cost/ or economic aspect/ or economic evaluation/ or economics/ or fee/ or funding/ or "health care cost"/ or "health care financing"/ or "health economics"/ or "hospital billing"/ or "hospital charge"/ or "hospital cost"/ or "hospital finance"/ or "hospitalization cost"/ or "insurance"/ or "investment"/ or "medical fee"/ or "nursing cost"/ or "pharmacoeconomics"/ or "resource allocation"/ or "resource management"/ or "tax"/ or exp "health insurance"/ or pharmacoeconomics.fs. or (cost adj1 effectiv$).mp.

Appendix 2: Flow Chart



Appendix 3: Detailed Overview of Methods and Results for Review of Economic Evaluations

STUDY			METHODS								RESULTS						UNCERTAINTY		NOTES	
Authors	Country	Target Population	Study Type	Perspective	Time Horizon	Model Type	Outcomes: Cost	Outcomes: Health	Discounting	Data Sources	Cost (per person)	Health Outcome (per person)	ICER	CE@ 1xGDP/capita	CE@ 50k	CE@ 3xGDP/capita	PSA: %CE	DSA: key variables	Industry-sponsored	Other
Najafzadeh 2009 (28)	Canada	≥60 y prevalent cohort	CUA	HCP	lifetime	DES	Intervention ($150) HC resource use	QALYs	Cost: 5% QALYs: 5%	Clinical: Shingles trial QALYs: literature Cost: BC admin data	Vaccinated: $251 ($205, $318) Non-Vaccinated: $136 ($84, $206) Incremental: $115 ($53, $174)	[QALYs lost] Vaccinated: 0.0044 (0.0010, 0.0107) Non-Vaccinated: 0.0072 (0.0019, 0.0161) Incremental: 0.0028 (-0.0018, 0.0092)	$41,709	No	Yes	Yes	52% @$50k 71% @$100k	Age at vaccination Average PHN length Waning of vaccine protection QALY weight for HZ pain QALY weight for PHN Vaccine cost	No	DES-description seems more like a Markov model
Brisson 2008 (23)	Canada	65 y incident cohort	CUA	HCP	lifetime	Cohort	Intervention ($150) HC resource use	QALYs	Cost: 5% QALYs: 5%	Clinical: Shingles trial, admin data QALYs: literature Cost: admin data, literature	Incremental: $104	Incremental: 0.0031	$33,152	Yes	Yes	Yes	70% @$40k 90% @$50k	Age at vaccination Waning of vaccine protection PHN vaccine efficacy QALY weight for PHN Vaccine cost	Yes	unusual way to determine vaccine efficacy; provide data for different combinations of age at vaccination and vaccine price

STUDY			METHODS								RESULTS						UNCERTAINTY		NOTES	
Authors	Country	Target Population	Study Type	Perspective	Time Horizon	Model Type	Outcomes: Cost	Outcomes: Health	Discounting	Data Sources	Cost (per person)	Health Outcome (per person)	ICER	CE@ 1xGDP/capita	CE@ 50k	CE@ 3xGDP/capita	PSA: %CE	DSA: key variables	Industry-sponsored	Other
Moore 2010 (24)	UK	≥50 y prevalent cohort	CUA	HCP	lifetime	Markov	Intervention (£95) HC resource use	QALYs	Cost: 3.5% QALYs: 3.5%	Clinical: Shingles trial, literature (GPRD) QALYs: literature Cost: admin data, literature (GPRD)	NR Incremental (estimated): £38	Incremental: 0.0029	£13,077	Yes	Yes	Yes	93% @£30k	Age at vaccination Waning of vaccine protection PHN duration and split QALY weights for HZ and PHN pain Discount Rate	Yes	also present data from societal perspective (CE, not dominant); 40% vaccine coverage, though not relevant for incremental analysis
van Hoek 2009 (29)	UK	65 y incident cohort	CUA	HCP	lifetime	Markov	Intervention (£55) HC resource use	QALYs	Cost: 3.5% QALYs: 3.5%	Clinical: Shingles trial, literature (GPRD) QALYs: literature Cost: admin data	NR	NR	£20,412	Yes	Yes	Yes	87% @£30k	Age at vaccination Vaccine efficacy (direct/indirect protection, waning) PHN-associated burden of disease	No	also present booster dose scenario

STUDY			METHODS								RESULTS						UNCERTAINTY		NOTES	
Authors	Country	Target Population	Study Type	Perspective	Time Horizon	Model Type	Outcomes: Cost	Outcomes: Health	Discounting	Data Sources	Cost (per person)	Health Outcome (per person)	ICER	CE@ 1xGDP/capita	CE@ 50k	CE@ 3xGDP/capita	PSA: %CE	DSA: key variables	Industry-sponsored	Other
Bilcke 2012 (27)	Belgium	60 y incident cohort	CUA	HCP	lifetime	Markov	Intervention (€90) HC resource use	QALYs	Cost: 3% QALYs: 1.5%	Clinical: Shingles trial, admin data, literature QALYs: literature Cost: literature (survey)	Most in favor of vaccination [costs for cohort, cohort size NR] Incremental: €3,505,428 Least in favor of vaccination [costs for cohort, cohort size NR] Incremental: €1,759,838	Most in favor of vaccination [QALYs for cohort, cohort size NR] Incremental: 1,406 Least in favor of vaccination [QALYs for cohort, cohort size NR] Incremental: 72	Most in favor of vaccination: €1,251 Least in favor of vaccination: €48,975	Most in favor of vaccination: Yes Least in favor of vaccination: No	Most in favor of vaccination: Yes Least in favor of vaccination: No	Most in favor of vaccination: Yes Least in favor of vaccination: Yes	NA	SOI (severity of illness) score Waning of vaccine protection All persons vs. immunocompetent only Age at vaccination Vaccine efficacy	No	present results for different age groups
Annemans 2010 (22)	Belgium	≥60 y prevalent cohort	CUA	HCP	lifetime	Markov	Intervention (€141.18) HC resource use	QALYs	Cost: 3% QALYs: 1.5%	Clinical: Shingles trial, survey, literature QALYs: literature Cost: expert panel	[costs for cohort, cohort size NR] Incremental: €51,640,533	[QALYs for cohort, cohort size NR] Incremental: 7,595	€ 6,799	Yes	Yes	Yes	95% @1xGDP/cap	PHN-associated burden of illness Discount rate Waning of vaccine protection QALY weights Vaccine cost	Yes	also present societal perspective

STUDY			METHODS								RESULTS						UNCERTAINTY		NOTES	
Authors	Country	Target Population	Study Type	Perspective	Time Horizon	Model Type	Outcomes: Cost	Outcomes: Health	Discounting	Data Sources	Cost (per person)	Health Outcome (per person)	ICER	CE@ 1xGDP/capita	CE@ 50k	CE@ 3xGDP/capita	PSA: %CE	DSA: key variables	Industry-sponsored	Other
van Lier 2010 (32)	Netherlands	70 y incident cohort	CUA	SP	lifetime	Markov	Intervention (€77) HC resource use	QALYs	Cost: 4% QALYs: 1.5%	Clinical: Shingles trial, admin data, literature QALYs: literature Cost: admin data, literature (survey)	[costs for cohort, cohort size NR; direct medical care cost only, no vaccine cost] Vaccinated: €1,082,777 Non-Vaccinated: €1,306,022 Incremental: €223,245	[QALYs for cohort, cohort size NR] Vaccinated: 1,350 Non-Vaccinated: 1,703 Incremental: 352	€ 21,716	Yes	Yes	Yes	NA	Discount rate Vaccine cost Waning of vaccine protection Age at vaccination	No	also present societal perspective, different age groups
Szucs 2011 (26)	Switzerland	70-79 y	CUA	HCP	lifetime	Markov	Intervention (CHF240.70) HC resource use	QALYs	Cost: 3.5% QALYs: 1.5%	Clinical: Shingles trial, surveillance data, literature QALYs: literature Cost: literature (Swiss HZ and PHN BOI study)	[costs for cohort, cohort size NR] Incremental: CHF22,600,000	[QALYs for cohort, cohort size NR] Incremental: 885	CHF25,538	Yes	Yes	Yes	NA	Discount rate incidence Waning of vaccine protection Vaccine cost QALY weights	Yes	also present societal perspective

STUDY			METHODS								RESULTS						UNCERTAINTY		NOTES	
Authors	Country	Target Population	Study Type	Perspective	Time Horizon	Model Type	Outcomes: Cost	Outcomes: Health	Discounting	Data Sources	Cost (per person)	Health Outcome (per person)	ICER	CE@ 1xGDP/capita	CE@ 50k	CE@ 3xGDP/capita	PSA: %CE	DSA: key variables	Industry-sponsored	Other
Pellissier 2007 (25)	US	≥60 y prevalent cohort	CUA	HCP	lifetime	Cohort	Intervention (US$150) HC resource use	QALYs	Cost: 3% QALYs: 3%	Clinical: Shingles trial, literature QALYs: literature Cost: admin data, literature	Incremental: US$104 (US$33, US$216)	Incremental: 0.0041 (0.0024, 0.0058)	US$18,439	Yes	Yes	Yes	94% @US$50k >99% @US$100k	Vaccine cost PHN cost Waning of vaccine protection QALY weight PHN and HZ vaccine efficacy Complication cost	Yes	used all HZ data (not only immunocompetent individuals) for base case analysis
Rothberg 2007 (31)	US	60 y incident cohort	CUA	SP	lifetime	Markov	Intervention (US$145) HC resource use Prroductivity loss	QALYs	Cost: 3% QALYs: 3%	Clinical: Shingles trial, literature QALYs: literature Cost: literature	Male Vaccinated: US$263 Non-Vaccinated: US$155 Incremental: US$108 Female Vaccinated: US$334 Non-Vaccinated: US$240 Incremental: US$94	[QALE] Male Vaccinated: 11.2910 Non-Vaccinated: 11.2903 Incremental: 0.0008 Female Vaccinated: 13.1439 Non-Vaccinated: 13.1429 Incremental: 0.0011	Male US$143,721 Female US$89,566	No	No	Male: No Female: Yes	NA	Age at vaccination Vaccine cost Vaccine efficacy PHN-associated burden of disease	No	conservative analysis, no reduction in PHN beyond the reduction in HZ incidence; CE @US$50 for 70 year old women and @US$100k for 65-75 year old men and 60-75 year old women

STUDY			METHODS								RESULTS						UNCERTAINTY		NOTES	
Authors	Country	Target Population	Study Type	Perspective	Time Horizon	Model Type	Outcomes: Cost	Outcomes: Health	Discounting	Data Sources	Cost (per person)	Health Outcome (per person)	ICER	CE@ 1xGDP/capita	CE@ 50k	CE@ 3xGDP/capita	PSA: %CE	DSA: key variables	Industry-sponsored	Other
Hornberger 2006 (30)	US	≥60 y prevalent cohort, history of VZV infection	CUA	SP	lifetime	Markov	Intervention (US$50-500) HC resource use Prroductivity loss	QALYs	Cost: 3% QALYs: 3%	Clinical: Shingles trial, literature QALYs: literature Cost: admin data, literature	[Direct medical care cost only, no vaccine cost] Vaccinated: US$61 Non-Vaccinated: US$98 Incremental: US$37	[QALE] Vaccinated: 9.9095 Non-Vaccinated: 9.9111 Incremental: 0.0016	[Vaccine cost $100, duration of protection 12 years] US$61,875	No	No	Yes	60% @US$50k 74% @US$100k	Age at vaccination Vaccine cost QALY weight for HZ and PHN Waning of vaccine protection Time horizon	No	It seems that PSA varied all variables, including age

CUA, Cost-utility analysis; HCP, health care payer perspective; HZ, herpes zoster; ICER, incremental cost-effectiveness ratio; CE, cost-effective; DES, discrete event simulation; GDP, gross domestic product; PSA, probabilistic sensitivity analysis; QALE, quality-adjusted life expectancy; QALY, quality-adjusted life years; SP, societal perspective; DSA, Deterministic Sensitivity Analysis.

Notes:

- Moore, Annemans, and Szucs use the same, industry-developed, model
- van Hoek and van Lier use the same model
- Exchange rates:
  - 1 GBP = 1.5967 C$
  - 1 EUR = 1.2952 C$
  - 1 CHF = 1.0784 C$

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