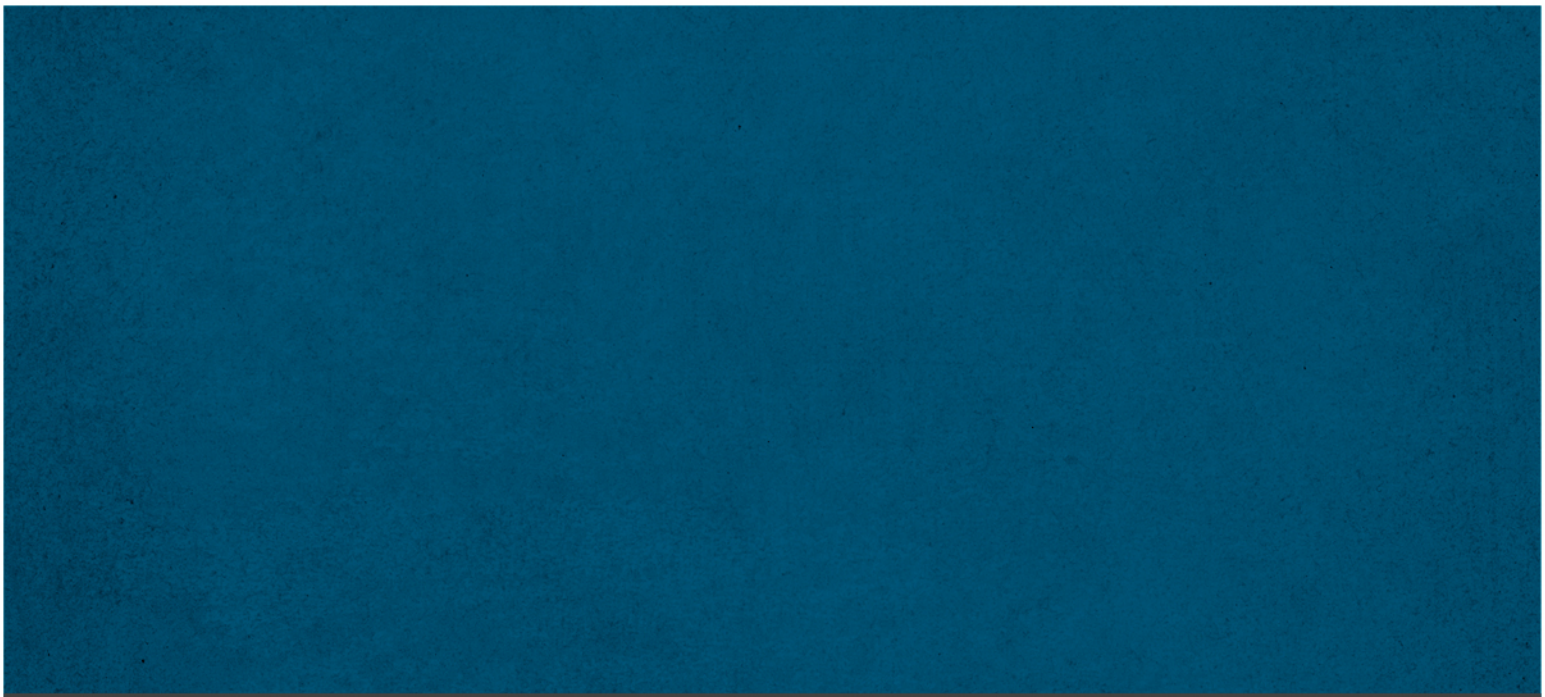
RECOMMENDATIONS FOR ZOSTER IMMUNIZATION PROGRAMS

CANADIAN IMMUNIZATION COMMITTEE



PROTECTING CANADIANS FROM ILLNESS

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Canada

TO PROMOTE AND PROTECT THE HEALTH OF CANADIANS THROUGH LEADERSHIP, PARTNERSHIP, INNOVATION AND ACTION IN PUBLIC HEALTH.
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RECOMMANDATIONS POUR LES PROGRAMMES DE D'IMMUNIZATION CONTRE LE ZONA

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NATURE AND CHARACTERISTICS OF THE INFECTIVE AGENT

The varicella-zoster virus (VZV) is an enveloped double-stranded DNA virus of the Herpesviridae family. VZV infects more than 95% of North Americans (1). The virus causes two distinct clinical syndromes: varicella (chickenpox) and zoster (shingles).

CLINICAL MANIFESTATIONS AND COMPLICATIONS

Varicella, also known as chickenpox, is an acute illness characterized by fever and generalized, pruritic, vesicular rash, occurring mostly in non-immunized children. The incubation period is 14-21 days. Varicella is highly contagious and most readily communicable in the early stage of the eruption (2). The primary infection is varicella (1). In the pre-vaccine era, 90% or more of Canadian children were infected by 12 years of age (3). After varicella infection, VZV migrates via retrograde axonal transport to sensory ganglia, where it becomes latent (1). VZV can become reactivated; reactivations can be asymptomatic or symptomatic, leading to the development of herpes zoster. Zoster infection typically occurs many decades after primary infection with VZV, although it can occur earlier (1).

Zoster infection is characterized by neuropathic pain and a dermatomal rash, with a lifetime risk of 15-28% in Canada (3, 4). In one study, six percent of individuals experienced one or more recurrent episodes over an average follow-up period of 7.3 years (5). A typical zoster rash in an immunocompetent individual involves one or two adjacent dermatomes, and lasts 7-10 days (1, 6). Thoracic dermatomes are most frequently affected (50% of cases) (1). Nearly three of four patients report having prodromal pain, which can precede the rash by days to weeks (1, 7), or pain with no rash (zoster sine herpete) (7, 8). T-cell-mediated immunity to VZV antigens is more important than antibody levels in preventing the development of zoster; aging and immunosuppression result in a decline in VZV-specific cell-mediated immunity that predisposes to zoster (1, 9).

Complications occur in 13 to 40% of cases (10, 11). The most frequent complication of zoster is pain, divided into acute pain (within 30 days of rash onset), subacute pain (between 30 and 90 to 120 days), and postherpetic neuralgia (PHN), which is significant pain persisting longer than 90 to 120 days after rash onset (8, 12). PHN occurs in 10 to 70% of patients with zoster (13-15), in approximately 20% of adults overall, but in one-third or more of octogenarians (16). Other sources state that PHN occurs in one-third of zoster cases over age 60 (11, 13, 17). Regardless, the risk of PHN from zoster increases with age (1). Increased hospitalizations and medications for patients with PHN drive the overall cost of zoster (18). Treatment options for PHN are of limited effectiveness (19, 20). PHN frequently has a major adverse impact on quality of life, especially in elderly persons (21-23). There are many other complications of zoster infection such as loss of vision, facial paralysis and inflammation of the spinal cord and brain (24, 25). Sight-threatening eye infections (zoster ophthalmicus) can often result in keratitis, which occurs in 2/3 of patients with zoster ophthalmicus (1). In British Columbia from 2001 to 2003, 43.7% of all zoster hospitalizations had complications (26).

EPIDEMIOLOGY OF THE DISEASE

Incidence of zoster is increasing (26, 27) and has been since the 1980s (4). Increasing rates in the elderly are at least in part attributable to the aging of the population (4). However, hospitalization rates decreased between 1999 and 2003 (26). Zoster incidence ranges from 15 per 10,000 person-years to 34 per 10,000

person years overall (1, 28). In contrast, incidence for elderly patients ranges from 39 per 10,000 person years to 118 per 10,000 person years. Half of those who live to be 85 years old will experience an episode (1).

In a study using administrative data on zoster-related diagnosis performed by Edgar and colleagues in 2007, it was found that in British Columbia (BC) between 1994 and 2003, there were an average annual rate of 29 physician visits and one hospitalization per 10,000 population due to zoster. People 65 and older had higher incidence of both physician visits and hospitalizations (70 per 10,000 and 5 per 10,000 respectively). As well, during the same time period, there were an average of 11,460 physician visits (range 10,003-13,458) and 389 hospitalizations (range 300-450) per year in BC. More than half (54%) of physician visits were in those 50 years of age and older. Zoster was the underlying cause of 29 deaths in BC between 1994 and 2003. Twenty-eight of these deaths were in those 65 years of age and older; the mortality rate was 5.5 per million in this age group (26). In Manitoba, between 1979 and 1997, an increasing incidence of zoster was observed by examining physician billing claims and hospital separation data. Among the age groups 15–44, 45–64, and ≥65 years, the annual incidence was 19, 42, and 81 per 10,000 population, and the rate of hospitalization per 100 cases was 1, 2.8, and 10.6, respectively (4).

In Canada, with a population of approximately 30 million, each year it is estimated that there are 130,000 new cases of zoster, 17,000 cases of PHN and 20 deaths. This results in 252,000 physician consultations and 2000 hospitalizations (29). Over 5000 cases are in people who are at particular risk due to immunosuppression, and men and women are affected equally (30).

There is a hypothesis that with widespread varicella immunization and thus decreased varicella exposure, adults previously infected with VZV will be less likely to experience natural immune boosting from circulating wild-type VZV (31). The decreased opportunity for cell mediated immunity that results from periodic exposure to varicella may result in increasing rates of zoster in the future (1, 4, 7, 32-41). Some studies show early evidence of this (4, 26). However, others report no change in the incidence of zoster (42), or show an increase in incidence prior to the implementation of varicella immunization campaigns (4, 27, 43).

Multiple factors in addition to an aging population could contribute to changes in the incidence of zoster over time including changes in reporting or in diagnostic coding of zoster cases, or changes in risk factors for zoster over time (e.g., the use of steroids or immunosuppressive therapy) (44). There are no conclusive data about the impact of varicella immunization on age or rates of zoster, thus further studies on and more observation of the factors influencing the epidemiology of zoster will be useful (1, 31, 44). It is still too early in the vaccine era to be certain if an increase in zoster will occur as a result of varicella immunization (7).

SPECIFIC POPULATIONS AFFECTED AND RISK FACTORS

The elderly are more susceptible due to biological aging of cell-mediated immune responses (4, 9, 41). This is significant also due to the aging of the Canadian population; seniors (those older than 65 years) make up the fastest-growing age group (45).

Zoster rash may be atypical in the immunocompromised due to dissemination or chronicity. A laboratory diagnosis may be needed when atypical lesions are present to determine a causal agent (1, 6). In those with cellular immunodeficiencies such as HIV, hematological malignancies, solid tumors, and following cell or solid organ transplantation, VZV may lead to cutaneous dissemination and seeding of the internal organs (lungs, liver, intestine and brain) (1, 6). Such visceral dissemination is associated with a case fatality rate of 5 to 15% (1). The level of immunosuppression may alter the risk of developing these complications (46, 47). Others with immunosuppression due to arthritis or cancer may also be at increased risk of VZV infection. As well, female sex may be a risk factor for PHN (1).

Rates of PHN are higher in solid organ transplant patients compared to immunocompetent populations (47). Over 90% of adult solid organ transplant recipients will be seropositive for VZV. Zoster is a frequent infectious complication in solid organ transplant recipients, with an incidence of approximately 8-11% during the first 4 years post-transplant (46-48). Older transplant recipients are at greater risk for the development of zoster, and heart and lung transplant patients have increased rates of zoster compared to other transplant recipients, possibly related to more intensive immunosuppression (46-48). The length of immunosuppression is lifelong in most solid organ transplant patients, and thus the increased risk of zoster is continuous after transplantation (46-48).

CURRENT DISEASE TREATMENT AND PREVENTABILITY

Antiviral treatment for zoster aims to reduce viral replication, duration of rash and acute pain, as well as prevent complications that are more common in immunocompromised patients. It also accelerates rash healing (8), and early antiviral treatment may minimize the risk of developing PHN (1, 8). Therefore antiviral therapy should be initiated as soon as possible (8). In patients with unexplained and atypical local pain (possibly having zoster sine herpete), it has been suggested that antiviral therapy against VZV may be of benefit (8).

PERSONAL AND SOCIAL IMPACT OF THE DISEASE

The effects of PHN on quality of life are comparable to diabetes, myocardial infarction, congestive heart failure and depression (23). Nearly half of PHN patients report daily pain of moderate intensity; 20% report severe daily pain. Such pain causes significant decreases in daily activities, impaired sleep and clinical depression (30). Although zoster has similar rates of physician visits to varicella (32.5 and 28.9 per 10,000 population for varicella and zoster respectively), zoster infections are associated with a higher hospitalization rate than varicella (1.0 compared with 0.4/10,000 population) (26).

VACCINE CHARACTERISTICS

Zostavax® is a live, attenuated vaccine based on the Oka/Merck attenuated varicella virus strain which is also used for varicella vaccine production (49). Although zoster vaccine contains the same components as the varicella vaccine Varivax® (Merck), it has 14-fold or higher virus concentration (not less than 19,400 plaque forming units per dose). Varivax® and Zostavax® should therefore not be used interchangeably i.e., Varivax® should not be used for zoster prevention in older adults, and Zostavax® should not be used for prevention of varicella in children.

Zostavax® is a lyophilized (freeze-dried) product. To reconstitute a dose, the contents of the vial containing the lyophilized vaccine should be mixed with the entire volume of the supplied diluent for one dose. The diluent is sterile water for injection without preservatives or other additives. When reconstituted, the product is a semi-hazy to translucent off-white to pale yellow liquid. A reconstituted dose is about 0.65 ml. It is to be administered subcutaneously, preferably in the deltoid area of the upper arm.

Approved formats in Canada include packages of 1 or 10 doses, with the lyophilized component in a vial, and the diluent in either a vial or prefilled syringe. The stopper does not contain latex. Following reconstitution the vaccine may be stored at room temperature for up to 30 minutes prior to use.

Zoster vaccine must be transported and stored at a temperature of -15ºC or lower; diluent should not be frozen and should be kept at room temperatures of +20 to +25ºC or in the refrigerator at +2 to +8ºC. The provider should adhere to provincial / territorial guidelines for vaccine storage and handling, and contact their local health unit if the vaccine is exposed to temperature outside of the manufacturer recommended storage range (50). Merck had issued general stability information in the past (i.e., the vaccine may be

stored and/or transported at refrigerator temperature (2 to 8ºC) for up to 72 continuous hours prior to reconstitution (51)). However, in July 2012, Merck retracted this information and stated that it can no

longer support previously issued stability information or issue new general stability information in light of a change in Merck's Global Stability Policy (52). Reconstituted vaccine must not be frozen. Appropriate freezers for storage include those with separate freezer compartments with sealed doors and include those which are frost free.

VACCINE EFFICACY AND EFFECTIVENESS

The efficacy of the vaccine has been demonstrated in a large phase III trial conducted in the US, known as the Shingles Prevention Study (15). In this trial, 38,546 healthy adults aged ≥ 60 years who had a previous history of chickenpox infection but no history of shingles and were not immunocompromised were randomized to receive vaccine or placebo. The follow-up time period was a median of 3.1 years. Overall vaccine efficacy was 61.1% (95% CI, 51.1-69.1%) for burden-of-illness score which was a combined measure of incidence and severity as assessed by a validated quality of life index; this was higher in the younger than in the older group (60-69 years: 65.5 (95% CI,51.5–75.5), 70+ years: 55.4 (95% CI,39.9–66.9)). Efficacy was 51.3% (95% CI, 44.2–57.6%) for confirmed zoster incidence (95% CI 44.2-57.6). This efficacy was lower in the older age group, at 37.6% among subjects 70 years of age or older compared to 63.9% in those 60-69 years old (P<0.001). Efficacy for prevention of post-herpetic neuralgia was 66.5% (95% CI, 47.5–79.2%), and was also demonstrated in the older age group (60-69 years: 65.7% (95% CI, 20.4–86.7%), 70+ years: 66.8% (95% CI, 43.3–81.3%)).

A new phase III study was published in the spring of 2012, involving 22,439 subjects aged 50–59 years in North America and Europe. The subjects were given one dose of Zostavax®, and followed for occurrence of herpes zoster for a mean of 1.3 years. Vaccine efficacy for preventing herpes zoster was reported at 69.8% (95% CI, 54.1–80.6) (53).

Vaccine efficacy estimates typically generated from phase III clinical trials need to be substantiated by vaccine effectiveness estimates which typically originate from studies conducted in the post-marketing phase. There are currently no published post-marketing trials for zoster vaccine. Therefore, the vaccine effectiveness used in the cost models is estimated from the phase III observed vaccine efficacy estimates. Because of some restrictions on inclusion of study participants in the Shingles Prevention Study, it is possible that vaccine effectiveness may be lower when the vaccine is used in the broader population. Herd immunity is not expected with broad use of zoster vaccine which prevents reactivation of latent herpes infections but does not interrupt transmission, as primary chickenpox infections originating from index cases with zoster are uncommon. It will be important to keep abreast of studies of zoster vaccine effectiveness in the future, as this parameter along with duration of protection described below, are key input assumptions that affect results of the incremental cost effectiveness ratios for organized publicly funded programs using zoster vaccine.

DURATION OF PROTECTION

Duration of protection was studied in the Shingles Prevention Study cohort and shown to persist for 4 years. A Short-Term Persistence Substudy, which re-enrolled 7320 vaccine and 6950 placebo recipients from the 38,546-subject Shingles Prevention Study population, studied duration of protection for years 5-7 after immunization. The results indicate that protection persists for 7 years following immunization for both incident zoster and for zoster burden of illness. Sustained protection against zoster as assessed by burden of illness was 50.1% (95% CI, 14.1-71.0), against herpes zoster was 39.6% (95% CI, 18.2–55.5), and against post-herpetic neuralgia at 60.1% (95% CI, –9.8 to 86.7) (54). Lack of efficacy for post herpetic neuralgia was hampered by small numbers of these cases (n=19) because of the cross-over study design, resulting in the wide confidence intervals. Vaccine efficacy for the combined study results (Shingles Prevention Study plus Short-Term Persistence Substudy) was 58.6% (95% CI, 48.6–66.6) for

herpes zoster burden of illness, 64.9% (95% CI, 47.4–77.0) for the incidence of PHN, and 48.7% (95% CI, 42.0–54.7) for the incidence of herpes zoster (54). Follow-up is being conducted out to 10 years (55). At this time, it is not known whether booster doses will be recommended in the future.

SEROLOGIC TESTING

Immune protection against shingles before or after immunization cannot be readily tested using commercially available laboratory tests. Therefore, there is no role for post-immunization testing of antibody titres. As well, there are no accepted correlates of protection against varicella and zoster using either tests for humoral antibody or cell mediated immunity; the latter is believed to be the key protective mechanism.

NACI RECOMMENDATIONS FOR USE OF ZOSTER VACCINE

Zostavax® was approved for persons 60 years and older in August 2008 and approval was extended to those aged 50 to 59 years in May 2011. In its 2013 statement, the Canadian National Advisory Committee on Immunization (NACI) recommends zoster vaccine for the prevention of herpes zoster and its complications in persons 60 years and older without contraindications and recommends that it may be used in those aged 50-59 years (56). These recommendations remain unchanged from NACI's previous Zoster statement, published in 2010 (44).

NACI recommends that zoster vaccine may be administered to those with a prior history of shingles. A cross-over placebo controlled trial of 101 subjects aged 50 and older found that systemic adverse events were comparable in vaccine and placebo recipients (57). Efficacy against prevention of further episodes of zoster in people with a prior episode of zoster is unknown as the Shingles Prevention Study excluded enrolees with a prior history of shingles.

NACI has also recommended that zoster vaccine should be administered to patients indicated for vaccine irrespective of a prior history of chickenpox or documented prior varicella infection (44, 58). Given that nearly all Canadians indicated for immunization will have had prior chickenpox exposure even if a prior diagnosis of VZV cannot be recalled, routine testing for varicella antibody is not recommended. There is no known safety risk associated with immunization of healthy individuals who are susceptible. In the rare circumstance that patients are known to be serologically varicella susceptible based on previous testing for another reason, they should be immunized with 2 doses of varicella vaccine, in keeping with current guidelines for varicella immunization (59).

CONTRAINDICATIONS

Systemic hypersensitivity to gelatin or neomycin are contraindications to receipt of Zostavax® as both of these non-medicinal ingredients are contained in the product. Contact dermatitis to neomycin is not a contraindication. Other contraindications include primary and acquired immunodeficiency, high dose immunosuppressive therapy, active untreated tuberculosis and pregnancy. Additional details of these are provided in the 2013 and 2010 NACI statements and the product monographs cited previously. A heat inactivated zoster vaccine is under development and in the future, will have application in immunocompromised individuals. The live attenuated zoster vaccine is not contraindicated in those on replacement steroids being treated for adrenal insufficiently, or low dose systemic, topical or inhaled steroids. The 2013 NACI statement (56) provides additional recommendations and contraindications in relation to the immunization of:

- individuals with a history of herpes zoster ophthalmicus;
- individuals with HIV, or post-organ or hematopoietic stem cell transplants, or individuals receiving high dose corticosteroids, chemotherapy or immune suppressing medications;
- individuals on anti-TNF biologics.

SAFETY

Safety of the vaccine has been most closely examined in the cohort of recipients in the Shingles Prevention Study cited above, and a safety substudy (60). The latter study included serious outcome surveillance in all participants and a detailed review of adverse events in a substudy of 6616 recipients. Selection of participants for the substudy was not randomized and was voluntary; it included detailed symptom recording for 42 days following vaccine receipt. All participants were followed for serious events in the first 42 days after immunization; thereafter, only deaths and serious events that were definitely, probably and possibly related to vaccine were reported from each site. After inoculation, the same proportion of vaccine and placebo recipients reported serious adverse events (255 (1.4%) vaccine recipients and 254 (1.4%) placebo recipients). This lack of a difference was also observed in the group aged 80 years and older. Local inoculation-site side effects were reported by 1604 (48%) vaccine recipients and 539 (16%) placebo recipients in the substudy. A varicella-like rash, defined as 1 or more ungrouped vesicles, occurred at the inoculation site more frequently in vaccine recipients than placebo recipients (0.11% vs. 0.04%), however, neither wild type nor vaccine strain varicella virus were identified from any of these lesions by culture or PCR and no cases of disseminated vesicular disease caused by the vaccine virus were observed. Erythema and swelling at the injection site were the only events that were more intense among vaccine recipients compared to placebo. These were reported as severe in less than 1% of vaccine recipients. Erythema, swelling, pain and tenderness, and warmth at the injection site persisted longer in vaccine than in placebo recipients, with erythema persisting longer in younger vaccine recipients. Pruritus at the injection site was reported in 1% of placebo recipients and in 9.5% and 4.6% of the vaccine recipients aged 60-69 and 70+ years, respectively. In follow-up over a mean of 3.39 years, rates of hospitalization or death did not differ between vaccine and placebo recipients.

CO-ADMINISTRATION WITH OTHER VACCINES AND ANTI-VIRAL MEDICATION EFFECTIVE AGAINST VZV

Shingles vaccine may be given at the same time as influenza and pneumococcal polysaccharide vaccines, which are indicated for individuals in the shingles eligible age group.

In a randomized multicentre trial during the 2004-2005 influenza season, 380 subjects received zoster vaccine and influenza vaccine sequentially or concomitantly (61). The vaccines were well tolerated in both groups and antibody responses to both vaccines were similar whether given sequentially or concomitantly.

Pneumococcal 23-valent polysaccharide (Pneumovax® 23) vaccine and the shingles vaccine may be administered concomitantly. This is supported by the 2012 NACI recommendations published in the Canadian Immunization Guide (62), as well as the 2013 NACI statement (56). This is a change from the 2010 NACI recommendations, which advised that zoster vaccine should be given at least 4 weeks apart from Pneumovax® 23. This previous recommendation was based on results of a randomized study of safety and immunogenicity of Zostavax® administered concomitantly versus sequentially with Pneumovax® 23, which found that the VZV GMT antibody response induced by zoster vaccine administered concomitantly was inferior to that induced nonconcomitantly (63). Concomitant administration did not affect the serological response to PPV antigens. However, the clinical significance of this finding is unclear because antibody titres are not known to correlate with protection against shingles. A more recent observational study was conducted using managed care organization administrative data and assessment of the incidence of herpes zoster after immunization in those given zoster vaccine on the same day as pneumococcal vaccine compared to those zoster vaccine recipients in whom pneumococcal vaccine had been given 30 days to 1 year before the zoster vaccine (64). There were 56 incident zoster cases in the concomitant immunization cohort and 58 in the nonconcomitant immunization cohort, yielding a zoster incidence of 4.54 (95% confidence interval [CI], 3.43–5.89) and 4.51 (95% CI, 3.42–5.83) per 1000 person-years, respectively. The hazard ratio comparing the incidence rate of zoster in the two cohorts was 1.19 (95% CI, 0.81–1.74) in the adjusted analysis. This study did not

demonstrate an increased risk of zoster in the population receiving zoster vaccine and pneumococcal vaccine concomitantly. On this basis and in order to avoid deferral of individuals from immunization with one or the other of these vaccines when indicated, as well as to avoid risking a lost opportunity to give vaccine to someone who may not return for follow up, the Canadian Immunization Committee (CIC) recommends that pneumococcal polysaccharide and zoster vaccines may be given at the same visit.

PRECAUTIONS

Individuals treated with systemically administered anti-viral drugs effective against varicella-zoster viruses within 2 days before to 14 days following receipt of zoster vaccine may have a suboptimal response to the vaccine through interference with live attenuated virus replication. A second dose of zoster vaccine may be administered 42 days after the first and at least 24 hours after completion of anti-viral treatment. Those on long term treatment with these drugs should have treatment interrupted for at least 24 hours prior to receipt of zoster vaccine. Apart from labelled indications for treatment of herpes, varicella and zoster infections, these drugs may also be used off label for treatment of acute retinal necrosis, prophylaxis of CMV infections in transplant patients, and hepatitis B.

IMMUNIZATION STRATEGIES AND PROGRAMS FOR ZOSTER VACCINE

The zoster vaccine is a relatively new vaccine for which there is limited experience with its use among the targeted population. Therefore, the gathering of information related to the best strategies to deliver this vaccine is somewhat limited. Although it has been licensed and used in the US since 2006, its use still remains marginal in Canada, mainly because of the cost of the vaccine and the need for transport and storage in the frozen state.

Most of the published material tends to link zoster vaccine use with good immunization practices for adults, which, in general, are not as well organized as immunization services for children. Also, the strategies to consider are closely linked to acceptability and availability of the vaccine, and to the availability of adequate storage units to maintain potency of the vaccine until administration.

The NACI zoster vaccine statements published in 2010 and 2013 do not address the issue of vaccine administration strategies. The US Advisory Committee on Immunization Practices (ACIP) recommendations for the prevention of herpes zoster state that the zoster vaccine should be offered to patients 60 years and older at their first available clinical encounter with their health care provider (65). Strategies to promote zoster immunization should be implemented, and include linking of delivery of the zoster vaccine to delivery of other indicated adult vaccines and preventive health interventions. In addition, nursing homes and long term care facilities should develop strategies for routine zoster immunization to those 60 years and older without contraindications.

In support of these recommendations issued by experts groups, several articles addressing issues related to the administration of the zoster vaccine were published. These include the important role of recommendations from health care providers in the uptake of the vaccine in older adults (66-68); the perceived barriers to physicians of zoster immunization, such as financial; the perceived need for the vaccine; and the unknown duration of protection (67, 69).

The burden of disease related to herpes zoster and PHN were identified as factors associated with the intention of the physician to recommend zoster immunization (69). On the other hand, several factors were identified as having a negative effect on the intention to immunize. These include the lack of data on the duration of protection; thinking that the storage of a frozen formulation is a definite barrier to implementation; thinking that patients do not need the vaccine; and believing that patients would not be willing to pay for the vaccine (69).

GOAL OF PREVENTION

Due to the natural history of herpes zoster disease, three potential indicators of herpes zoster in the population can be targeted for prevention by the current vaccine: the burden of illness (BOI), herpes zoster and PHN. Canada has prevention goals for varicella but not for zoster (70). The development of prevention goals for zoster would be important to guide implementation of public health programs.

ALTERNATIVE IMMUNIZATION STRATEGIES AND PROGRAMS FOR MEETING THE GOAL

Different strategies include the implementation of programs for introduction at a specific age or age group with or without a catch-up program for older seniors.

The zoster vaccine is presently approved for use for people aged 50 years and over. According to NACI, immunization is recommended beginning at age 60 years, and allowed for patients aged 50-59 years (56). One of the major cost impacts of implementing a zoster immunization program would be the inclusion of a catch-up program. In view of current cost concerns for vaccines in Canada, it is very unlikely that such a catch-up program would be feasible. Even if such a program were to be considered, many questions remain to be answered, such as determining which age group should be included in view of the decline in efficacy for the prevention of zoster but the maintained protection against PHN in older patients (71).

At the moment, booster doses of zoster vaccine are not recommended for healthy individuals. This recommendation may need to be revisited as further information becomes available. Inclusion of booster doses of zoster vaccine would have substantial additional cost implications for the program.

There are limited data on the safety of the administration of the available frozen formulation of the zoster vaccine to immunocompromised individuals, and therefore, limited specific recommendations exist (65). The future availability of a killed virus formulation of the zoster vaccine might allow for its use in this specific population (72).

PROGRAM DELIVERY STRATEGY OR SYSTEM

It is quite clear from available information in the scientific literature that for optimal uptake, the administration of the zoster vaccine needs to be linked to other immunization strategies or programs, such as influenza and pneumococcal immunization in older adults.

Available data (see co-administration with other vaccines and anti-viral medication effective against VZV section on page 9) indicates that zoster vaccine may be co-administered with trivalent influenza vaccine and with pneumococcal polysaccharide vaccine. Use of other influenza and pneumococcal vaccines in the future, such as adjuvanted or high titre influenza vaccines, or conjugate pneumococcal vaccine, will necessitate further studies on co-administration.

SPECIFIC PROGRAM OBJECTIVES IN TERMS OF REDUCTION OF INCIDENCE, COMPLICATIONS, SEQUELAE AND MORTALITY

The objective chosen for a zoster immunization program, whether prevention of zoster or prevention of post-herpetic neuralgia through immunization in a limited age span or a broader age group will be a factor in the cost-effectiveness of the program. Available cost effectiveness analyses indicate that immunization limited to those in their 60s may be most economically favourable (29). Duration of protection of the vaccine is not yet known.

SPECIFIC OPERATIONAL OBJECTIVES FOR IMMUNIZATION COVERAGE FOR DIFFERENT TARGET GROUPS, AND VACCINE WASTAGE

The presently available frozen formulation will most likely be a significant deterrent to the accessibility of the vaccine, even though data indicate that most vaccine delivery settings have a fridge with a separate freezer, which is considered adequate for the storage of the frozen zoster vaccine (73). In a study performed by Merck in 2009, only 8% of physicians were found to have a freezer suitable for storage (73); however, updated information from Merck as of October 2010 indicates that there are 1,558 Zostavax® distribution points in Canada, giving access to 60% of Canadians. Thirty-nine percent of distribution points are family physicians, and 61% of accounts are held by pharmacies (74).

Supply interruptions have occurred following introduction of the vaccine in Canada due to manufacturing challenges at Merck related to competing production priorities given to varicella and combination varicella vaccines (i.e., measles, mumps, rubella and varicella vaccine) (75). An adequate continuous supply of the vaccine has to be assured by the manufacturer before deciding on the implementation of a zoster immunization program.

A refrigerator-stable formulation of Merck's zoster vaccine has been approved for use by Health Canada, but is not presently marketed (76). It is currently projected that this formulation will be available in Canada starting March 2014 (77). This refrigerated formulation might improve availability of the vaccine for the targeted groups due to ease of storage, as the storage conditions will be similar to other vaccines (50).

The objectives of vaccine coverage would be dependent on the objectives of the program. Coverage with influenza and pneumococcal vaccines among seniors based on the most recent national survey data in Canada are estimated at 67% and 34%, respectively (78). Influenza vaccine is given annually and pneumococcal vaccine is recommended once for most adults (79). Achievable zoster vaccine coverage may be at least as high as that for pneumococcal disease because of multiple opportunities (e.g., with annual influenza vaccine) for its administration and evidence of interest in receiving the vaccine by over a third of older individuals if offered at no charge (see Feasibility and Acceptability of a Zoster Vaccine Alternative Programs section below on page 17). In the US, the National Immunization Survey conducted in 2007 showed an uptake of only 1.9% in the six months after ACIP published its recommendations for the use of the zoster vaccine, but before its publication in the MMWR (80). In an update to this survey recently published, the immunization coverage was up to 6.7% by 2008 (81).

SOCIAL AND ECONOMIC COSTS AND BENEFITS

ECONOMIC IMPACT OF THE DISEASE

Canadian hospitalizations for zoster and PHN cost approximately $67 million to $82 million annually (1, 7, 82). Most of the disease is in adults over 60 years of age (82).

The economic burden of zoster in the elderly includes direct costs attributed to health-care use and indirect costs attributed to losses in productivity from temporary or more permanent disability, though given the age group primarily affected, indirect costs and lost productivity are expected to be less than for a younger age group. The economic burden of zoster is borne by individual patients and the health care system and quality of life is negatively affected due to the sequelae or complications related to the disease (65).

SOCIAL IMPACT OF THE DISEASE

There is no proven herd immunity generated by this particular vaccine, and only those that receive zoster vaccine will benefit by prevention of shingles with no expectation of indirect protection against shingles in non-immunized people. However, reduced zoster and PHN cases, increased quality of life, and decreased medical related costs are beneficial to immunized individuals, to society including families of cases, and to the medical community (83). Repeat physician appointments, prescription antivirals and analgesics, and potential work loss for those still employed are examples of social medical-related costs that may promote the uptake of the vaccine among those who choose to purchase the vaccine. The main benefits of zoster vaccine are the prevention of morbidity caused by PHN pain (rather than mortality from zoster disease) (29) and avoiding QALY[1] loss due to PHN (84). Of note as well is that the estimated number needed to immunize to prevent one zoster case is 11 persons, to prevent one case of PHN is 43 persons, to prevent one zoster-related death is 23,319 persons, to prevent one life year lost is 3,762 persons, and to prevent one QALY lost is 165 persons (29).

COST-EFFECTIVENESS ANALYSES[2] (85)

Cost-effectiveness analysis is a necessary category in the vaccine analysis framework to justify new immunization programs due to potential long-term and recurrent expenditures (86). A cost-effectiveness analysis is a type of economic analysis in which costs associated with two or more strategies are compared based on some measure of effectiveness[3](87). Cost-effectiveness of immunization programs is assessed using economic evaluations that synthesize clinical, epidemiological and economic information. The outcomes of cost-effectiveness analyses are expressed as incremental cost-effectiveness ratios (ICERs) relative to the current practice or alternatives per health effect (i.e., QALY gained, DALY[4] averted) (88).

In the summer of 2013, Forget, Peden and Strobel performed a critical assessment and review of studies on the cost effectiveness of zoster immunization (85). This work was completed for the CIC, and was conducted with the International Centre for Infectious Diseases (ICID). The review examined twelve publications from seven countries and summarized the evidence about the cost-effectiveness of the zoster vaccine, and the implications for Canadian public health policy makers.

Appendix 1 presents each study, the country in which it was conducted, the type of model, the perspective chosen, the time frame and analytical horizon, the main outcomes and the funding source and associated conflicts. Cost effectiveness ratios are translated into 2012 Canadian dollars using standard methods[5]. This conversion allows comparison across countries and over time because results are adjusted for both currency differences and inflation (85). All of the articles used epidemiological cohort models to assess cost effectiveness, and most used Markov decision-analytic models[6]. Costs were assessed from a variety of perspectives: third- party payer (TPP)[7], healthcare (HC)[8]

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[1] QALY is a quality-adjusted life year, or a year of life lived in perfect health.
[2] Analysis for the cost-effectiveness of zoster immunization has been provided by a critical assessment and literature review conducted by Forget, Peden and Strobel with the International Centre for Infectious Diseases, 2013.
[3] Effectiveness is the performance of health interventions in the real world.
[4] DALY is a disability-adjusted life year. It is a measure of overall disease burden, expressed as the number of years lost due to ill-health, disability or early death.
[5] An annual average “official exchange rate” is reported by the Bank of Canada: http://www.bankofcanada.ca/rates/exchange/exchange-rates-in-pdf/ (accessed 09/08/13). The “consumer price index” annual series is reported by the Bank of Canada: http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/econ46a-eng.htm (accessed 09/08/13).
[6] A Markov model is a decision analysis model that incorporates an element of time.
[7] Third-party payer is equivalent to the healthcare insurer and costs paid by the healthcare insurer may not capture all healthcare costs in some European countries because the state insurer requires co-payments.
[8] A HC perspective includes co-payments not captured in third-party payer perspective.

and societal[9]. The perspective chosen influenced which costs were included, and consequently the costs per QALY (85). All of the studies were based on the assumption of a single dose immunization in the base case, and costs and benefits were assessed over the expected lifetime.

Appendix 2 portrays the sources for the epidemiological data, as well as the input parameters – basic assumptions about vaccine efficacy and duration of protection, vaccine coverage and the method by which the study estimated the QALY decrements associated with zoster and PHN (85). An important input parameter is the proportion of HZ cases that develop PHN. This is because most of the benefits of the vaccine are seen in a reduction in the length and severity of pain associated with PHN. Some studies use the Shingles Prevention Study (SPS) as the source for the data, others use country specific data, while others base their analyses on a UK study that makes use of the General Practice Research Database (GPRD) (89).

Appendix 3 summarizes the various assumptions made about costs. Cost-effectiveness results are very sensitive to assumptions made about the price of the vaccine and the discount rate (85). Decision makers need to be aware of the important impact that vaccine price has on cost-effectiveness. All costs are presented in local currency, and then vaccine cost is translated into 2012 Canadian dollars. Some studies included vaccine administration costs directly and others reported administration costs separately. Where possible, vaccine administration costs are reported as a second figure in column 3. An important input parameter shown in Appendix 3 is the discount rate; different assumptions are made about discount rates, as jurisdictions have varying guidelines (85). Costs, and especially benefits in terms of improvements in the quality of life and reduced healthcare costs for treating disease complications, tend to be discounted at a higher rate in Canada than in Europe. This has the effect of reducing the estimates of cost effectiveness for Canada compared to Europe. Nevertheless, Canadian, American and British studies that assumed higher discount rates and outcomes are still cost effective (85).

The choice of cost-effectiveness threshold – the threshold below which an immunization program will be considered cost effective – is a policy decision. The threshold is a policy variable that ranges considerably, and a universally agreed upon threshold for an acceptable cost-effectiveness ratio for immunization programs does not exist (88, 90). Cost-effectiveness thresholds are often proposed by decision makers and vary across countries, from the very low €20,000 in the Netherlands (CAD 27,460) (91) to the £30,000 to £40,000 (CAD 47,895 to CAD 63,809) in the UK to the $50,000 to $100,000 (USD) in the USA. Canada, like many jurisdictions, does not have an official cost-effectiveness threshold, although the figure of $50,000 and $100,000 is often cited informally (92, 93). The World Health Organization (WHO) promotes the use of Gross Domestic Product (GDP) per capita, suggesting that those interventions that cost less than GDP per capita are highly cost effective, those between one and three times GDP per capita are cost effective and interventions that cost more than three times GDP per capita are not cost effective (94). This generates a higher threshold in richer countries that can afford to pay more to support the health of its citizens. Canadian per capita GDP in 2012 was just over $50,000, so the upper threshold according to the WHO proposed standard would be close to $150,000 per QALY.

Table 1 categorizes the various studies into those that generated cost per QALY estimates of less than $50,000 Canadian dollars, between $50,000 and $100,000 Canadian dollars, between $100,000 and $150,000 and more than $150,000. These align with WHO guidelines (94), and correspond with highly cost-effective, cost-effective and not cost-effective outcomes. Estimates from a single study may appear in more than one column depending on such factors as the age of immunization or the length of protection offered by the vaccine (85).

[9] A societal perspective includes productivity losses associated with time off work. Most of the articles that considered productivity losses assumed workforce participation ceases at age 70.

TABLE 1: ESTIMATED COSTS PER QALY (IN 2012 CANADIAN DOLLARS) (85)

Highly Cost- Effective	Cost-Effective		Not Cost-Effective
< $50,000	**$51,000 – $100,000**	**$101,000 - $150,000**	**> $150,000**
Annemans (95) Bilcke: all ages "best case" (96) Edmunds: > 2.5 years efficacy (97) Hornberger: 30 years efficacy (98) Moore: <85 years (83) Najafzadeh: <75 years (84) Szucs (99) Van Hoek: aged 65+ (100) Van Lier: ages 65+, 70+, 75+, 80+ (91)	Bilcke: ages 60 – 79 "worst case" (96) Edmunds: 2.5 years vaccine efficacy (97) Hornberger: 20 years efficacy (98) Moore: 85-89 years (83) Najafzadeh: 75+ years (84) Rothberg: aged 70+ (101) Van Hoek: aged 60+ (100) Van Lier: aged 60+ and 80+[10] (91)	Hornberger: <3 years efficacy (98) Moore: 90-94 years (83) Rothberg: females 60+ (101)	Bilcke: > 80 years in the "worst case" scenario (96) Moore: 95+ years (83) Rothberg: males 60+; males and females 80+ (101)

Table 1 thus shows that most of the studies, despite the range of underlying assumptions and variations in the models, conclude that zoster immunization is cost effective. Even when considering that in Canada the threshold of less than $50,000 per QALY is typically used (92, 93), most studies still indicate that zoster immunization is cost effective (see column 1 in Table 1). Costs exceeded $100,000 per QALY only when studies examined the cost effectiveness of the vaccine for people of very advanced ages (typically over 85 or 90 years of age) or when studies assume that vaccine efficacy will wane very rapidly after immunization (83, 96, 98, 101). Rapid waning of vaccine efficacy is not supported by the most recent evidence (85).

The costs of providing healthcare must also be considered. Healthcare costs vary across jurisdictions and Canadian healthcare costs fall between the lower costs associated with European studies and the higher costs in the United States. Across the entire range of costs, however, these studies suggest that zoster immunization is cost effective (85).

Cost-effectiveness results are very sensitive to the assumptions made about PHN incidence and persistence (85). This is an important issue because the cost associated with PHN and HZ is greatest among older people but the efficacy of the vaccine is greatest at younger ages. This in turn impacts the optimal target age group for immunization. If the protection offered by the vaccine is life long, it makes sense to immunize at younger ages. However, most of the benefits of the vaccine are seen in older people, among whom the incidence of PHN is higher. If waning is an issue, targeting the immunization to slightly older people may be more cost effective even though the efficacy of the vaccine will be lower. The more rapid the waning, the older the optimal target age group, other factors remaining unchanged (85). Only one of the studies considered the effect of a booster and found it not likely to be cost-effective (100).

[10] For those aged 80+, the ICER is $17,204 except under the extreme assumption that PHN burden is not reduced by the vaccine at all.

Table 2 shows that most of the evidence indicates that cost-effectiveness is maximized somewhere between the age 60 and 70 (85). Targeting younger or older age groups tends to be somewhat less cost effective. Evidence surrounding the optimal age of immunization is very sensitive to modeling assumptions. For example, if lost productivity associated with infection is taken into account, then immunizing a younger age group that is still in the labour force becomes more cost effective (85).

TABLE 2: COST PER QALY AT THE MOST COST-EFFECTIVE AGE (IN 2012 CANADIAN DOLLARS) (85)

Study	Most Cost-Effective Age	Cost-Effectiveness in CAD
Annemans 2010 (95)	65-69	9,932 (HC perspective)
Bilcke 2012 (96)	60-69	633/64,446 (best case/worst case)
Brisson 2008 (29)	N/A	N/A
Edmunds 2001 (97)	65+ (increases with age)	Lifelong Efficacy: 11,705 10 year efficacy: 28,552 2.5 year efficacy: 89,614
Hornberger 2006 (98)	considered 60+	C/E varies from 114,399 /QALY if vaccine wanes after 3 years, to 39,567 /QALY if protection lasts more than 30 years. At 20 years, C/E is 55,049/QALY
Moore 2010 (83)	65-69	23,984
Najafzadeh 2009 (84)	60-74	37,613
Pellissier 2007 (102)	considered 60+	23,242
Rothberg 2007 (101)	70+	Males: 90,907; Females: 60,073
Szucs 2011 (99)	60-69	18,241
Van Hoek 2009 (100)	70	35,355
Van Lier 2010 (91)	70	HZ alone/HZ+PHN: 35,405/16,077

Forget, Peden and Strobel conclude that the evidence, covering seven different countries conducted from three different perspectives and based on a variety of epidemiological and cost assumptions, suggests that a zoster immunization program is likely to be cost effective according to both the WHO proposed guidelines (94) and historical Canadian guidelines (85, 93). Cost-effectiveness is maximized between the age 60 and 70. Nearly all of the estimated cost-effectiveness ratios were under $100,000 per QALY, and some well under. These results are consistent with another published review of the literature (103). Despite the cost-effectiveness evidence, however, in the end it is the role of decision makers in each jurisdiction to decide whether the price of a given immunization program is one they are willing to pay.

FEASIBILITY AND ACCEPTABILITY OF A ZOSTER VACCINE PROGRAM

The number of people susceptible to zoster will increase steadily as the proportion of elderly persons and the number of immunocompromised patients increases in the population (104). Physicians perceive zoster-related morbidity as a great burden to the senior population (69). Individual quality of life among those with zoster is highly correlated with the severity of pain, which affects activities of daily living, and contributes to anxiety, depression and insomnia, which require additional medical management (105). The major gain of the vaccine is the reduction of burden of illness from zoster (100). The senior population, in which the vaccine is indicated for use, may be retired or still employed and may be a driving factor in zoster vaccine demand and uptake. The vaccine could possibly be integrated with existing programs and schedules for those ≥ 60 or 65 years (e.g., pneumococcal or seasonal influenza vaccines). Currently, the product monograph indicates that the vaccine cannot be co-administered with the pneumococcal polysaccharide 23 vaccine (49), suggesting that a second visit ≥ 4 weeks apart would be required (51). However, recent data suggests that the co-administration of these vaccines may not increase the risk of developing zoster (64) and co-administration is the preferred strategy. Inequity is created if patients cannot afford to purchase the vaccine (67).

Physician and pharmacist billing for prescription visits and/or administration of the zoster vaccine may be small in comparison to billing for other medical services, but it will still add additional cost to provincial health care systems. It is difficult to comment on or predict the prioritization of a publicly-funded zoster immunization program compared to other new vaccine programs or program expansions under consideration in any particular province or territory.

The presently available frozen formulation of the zoster vaccine also presents a feasibility issue. As previously discussed, appropriate freezers for storage include those with separate freezer compartments with sealed doors and include those which are frost free. Data indicate that most vaccine delivery settings have a fridge with a separate freezer (73); however, the requirement of a freezer may be a limiting factor in some jurisdictions.

Most people recover from zoster disease without long-term sequelae. There is conflicting information as to the actual degree of burden that zoster and PHN creates in society, although there are qualitative data about the negative impact on quality of life that this disease can cause. Initial efficacy and long-term effectiveness of the vaccine among those immunized requires further research, especially as waning immunity related with aging increases one's vulnerability for zoster and PHN. The age band of individuals that can be targeted with publicly funded vaccine at the outset of a zoster program is an important consideration not only because of vaccine effectiveness and therefore cost effectiveness differences by age, but total cost and vaccine supply issues.

Data on acceptability of the zoster vaccine is limited. In Québec, an immunization coverage survey done on the 2009-2010 A (H1N1) influenza vaccine, seasonal influenza vaccine and pneumococcal vaccine in persons aged 50 and over included a few questions on the patient's intention related to the zoster vaccine. In this survey, 37% of persons without prior history of zoster nor the vaccine strongly or mostly agreed with the statement that they intend to receive the zoster vaccine if offered at no charge. The intent dropped to 28% if the vaccine cost $150 (106).

A survey on knowledge, attitudes and beliefs of older Canadians and their healthcare providers regarding zoster and zoster vaccine showed that 87% of older Canadians were willing to receive the vaccine if it were recommended by a physician, and 93% of physicians were willing to recommend the vaccine. The vast majority of participants believed that the zoster vaccine should be publicly funded for all Canadians aged 60 and over, but 67% of older Canadians would be willing to pay for the vaccine if needed (107).

A study done in the Netherlands showed that 39% of invited patients accepted zoster vaccine when offered at no charge with influenza immunization (68).

ABILITY TO EVALUATE IMMUNIZATION PROGRAMS

Evaluation of newly implemented immunization programs is the duty of public health authorities and appropriate resources should be invested in monitoring systems and *ad hoc* studies. The evaluation of zoster immunization programs over time is extremely important, given the need to evaluate impact over the long term and, as with many other vaccine programs, the unknown duration of protection at the start of implementation. Monitoring and evaluating zoster immunization programs will require population-based reporting systems for zoster-associated diseases, and registries or information systems for follow-up of vaccine coverage (108). Effective linkage between the latter databases will also be important. Regular studies of the knowledge, attitudes and practices of the public and health professionals will also be necessary.

At a national level, much effort is still required to prepare for the evaluation of a new zoster immunization program, and few data are available in the literature. As for all immunization programs, provincial and national authorities will require a detailed evaluation plan for zoster immunization programs. Significant investments have to be made to conduct surveillance and program evaluation over the long term, and a multidisciplinary approach is needed.

AVAILABILITY OF INFORMATION SYSTEMS TO MEASURE COVERAGE, UTILIZATION, QUALITY

As with other health care programs, immunization is primarily a provincial and territorial responsibility. Each province and territory has its own data collection system – some are electronic, some are paper-based, and some jurisdictions do not routinely measure immunization coverage among adults. The model of vaccine delivery and reporting practices used by various providers in the jurisdiction, i.e., physician, public health, pharmacist or mixed, will also affect quality of coverage data.

It would be ideal to have a national zoster vaccine evaluation plan. It is known that adult immunizations are generally poorly recorded. It will be important to have adequate data captured of individual zoster immunizations in provincial/territorial registries due to the specific characteristics of this vaccine. Factors such as freezer stability, cost, goals of prevention and insufficient data on the need for booster doses mean that adherence to eligibility criteria and avoidance of duplication will be very important for this vaccine.

AVAILABILITY OF INFORMATION SYSTEMS FOR MONITORING REDUCTION OF DISEASE INCIDENCE, COMPLICATIONS, SEQUELAE, MORTALITY

Zoster is presently not a nationally notifiable disease. Shingles is not reportable in most provinces or territories of Canada, and there are limited data available in Canada on the prevalence, incidence or distribution of zoster in the population.

It would be desirable to have mechanisms for monitoring disease epidemiology that could be developed nationally for use in all jurisdictions. Some jurisdictions will possibly develop their own monitoring systems. Administrative data from medical diagnostic and hospital separation data has been used in several Canadian jurisdictions and may provide a source of data for monitoring trends over time. Linking

such data to immunization registries or other reliable sources of data on zoster vaccine receipt may provide opportunities for assessment of the impact of zoster vaccine.

AVAILABILITY OF SYSTEM FOR MONITORING ADVERSE EVENTS ASSOCIATED WITH VACCINE ADMINISTRATION

There is a national Canadian Adverse Event Following Immunization Surveillance System (CAEFISS) in which all Canadian jurisdictions participate, with reporting by health care providers including physicians, nurses and pharmacists. In six provinces the reporting of AEFI is under legislated mandates.

AVAILABILITY OF SYSTEMS FOR LINKING HEALTH OUTCOMES DATABASES, IMMUNIZATION REGISTRIES AND POPULATION REGISTRIES

The ability to issue personalized recalls to adult recipients of zoster vaccine should an additional dose of the vaccine be needed in the future would be preferable to the use of mass media and communication to immunization providers. Specific modalities to inform health authorities about zoster vaccine status should be considered before zoster program implementation. Development of immunization record repositories through linking to electronic medical records and public health immunization registries to support lifetime record keeping is a priority for optimal immunization program delivery and evaluation.

Evaluation of the zoster immunization program will be complex. Evaluation requires the development of a comprehensive plan and will demand significant resources.

RESEARCH QUESTIONS

The NACI Statements and various studies/articles by investigators identify knowledge gaps that require further research (15, 55, 56, 100, 109).

ONGOING AND PLANNED RESEARCH PROJECTS IN THE FIELDS OF VACCINE DEVELOPMENT, IMMUNOGENICITY, EFFICACY AND SAFETY

A zoster vaccine is under development by GlaxoSmithKline with Phase 3 trials in older adults (>50 years of age) and a phase 2 trial in those with immunocompromised including HIV infection and autologous hematopoietic stem cell transplant recipients (110, 111). This is an adjuvanted subunit vaccine using a proprietary adjuvant system AS01 (112). At this time, the proposed date of filing for approval by Health Canada is unknown.

The live attenuated zoster vaccine has a well-documented safety profile among those enrolled into clinical trials but questions remain to be answered, particularly in residents of nursing care facilities, the immunocompromised and patients with a history of herpes zoster (6, 57, 60, 113).

An inactivated heat stable varicella zoster vaccine is under development by Merck, with seven trials completed or ongoing. These include studies in both healthy and immunocompromised adults (114-120).

Additional studies to inform safety and effectiveness of vaccine co-administration with newer influenza vaccines and the conjugate pneumococcal vaccine are needed to inform recommendations for optimal zoster vaccine use in older adults.

Effectiveness of the zoster vaccine in the general population and the duration of protection and the need for repeat booster dosing are still unknown. Current studies in progress measuring the duration of zoster vaccine effectiveness have follow-up out to 7 years and will extend to 10 years.

NACI has stated that herpes zoster vaccine may be administered to individuals ≥50 years old with a prior history of herpes zoster. Based on expert opinion, it is recommended that the vaccine be given at least one year following the last episode of herpes zoster. No increase in adverse events has been observed in vaccine recipients with a prior history of herpes zoster. However, NACI recommends that determining the efficacy of herpes zoster vaccination in persons with a history of herpes zoster be a research priority (56).

The long term impact of varicella vaccine programs on zoster epidemiology should be studied, as available estimates from modeling have not been validated.

Use of vaccine and antivirals in the treatment of zoster and prevention of PHN is another area that needs more research.

As with other vaccines, there will need to be effectiveness research to determine if there has been a reduction in disease rates, burden of illness, and rates of PHN. In Canada, the public health burden of herpes zoster is not well described, nor are there registries to measure the incidence or prevalence. Questions still remain about the actual burden of PHN to individuals, society and the medical system and these are relevant to understanding cost-effectiveness.

RESEARCH TO ASSIST PLANNING, EVALUATION AND DECISION-MAKING

Further research will be required in order to inform planning of zoster immunization programs in the jurisdictions. The most effective model of delivery (i.e., public health and/or other immunization providers), and whether it is cost-effective to have catch-up programs may require economic analyses informed by mathematical modeling. Recommendations for the best strategies to reach the desired age group will help to promote vaccine uptake. Creative means for increasing the accessibility of zoster vaccine should also be developed.

Although reduction in cases of zoster is one of the most important long-term health outcomes, other endpoints are needed to monitor the short- and mid-term impact of immunization on PHN and zoster burden of illness. The overriding goals of prevention i.e., decreased cases of zoster or reduction in PHN or reduced burden of illness will need to be clarified.

In order to effectively use the currently marketed freezer stable vaccine throughout Canada, there needs to be an understanding of the freezer infrastructure at all levels of the vaccine distribution and storage system, taking into account a variety of provider types (50).

For practitioners, in relation to live vaccines generally, there is a need for clear definitions and guidelines related to the immunocompromised. It is especially relevant for zoster vaccine, given the age group for which the vaccine is intended. The current vaccine is contraindicated in immunocompromised individuals although ACIP provides specific recommendations for select use.

It is unknown presently whether the burden of disease and the impacts of zoster infection are different in subpopulations, such as immigrant and Aboriginal populations. Research is required to ensure that routine zoster immunization programs adequately meet the needs of those subpopulations.

OTHER CONSIDERATIONS

EQUITY AND ETHICAL CONSIDERATIONS

When making decisions related to prioritization of new immunization programs, provinces and territories may be faced with funding restrictions. In such instances, provinces and territories will have to carefully weigh the costs and benefits of each, and to consider other options to facilitate availability of vaccine if not publicly funded.

POLITICAL CONSIDERATIONS

The authority of the allocation of resources for vaccines may rest with various levels of government, and thus be outside of the control of provincial and territorial immunization program decision makers.

Based on available survey data in Canada, there is high support for this vaccine among the age group in question (106).

RECOMMENDATIONS

These recommendations from the Canadian Immunization Committee are based on the epidemiology of varicella zoster, zoster vaccine characteristics, disease modeling and economic analysis, as well as on the feasibility and acceptability of zoster immunization programs. Considerations related to these have been reviewed in preceding sections of this statement.

CIC recommends routine offering of zoster vaccine to immunocompetent adults without contraindications aged 60 or 65 years and older. Although the incidence and severity of herpes zoster begins to increase with age after 50 years and those aged ≥50 years may be expected to receive some benefit from immunization, the greatest benefit will be seen in those 60 years and older. As currently the duration of protection is unknown beyond 7 years, it is uncertain whether immunization at younger ages (such as beginning at age 50 years) will provide ongoing protection at older ages when the incidence of zoster is higher. Therefore, CIC does not recommend implementation of publicly funded programs for those below 60 years old at this time. In jurisdictions where targeting individuals at 60 years of age is deemed feasible because of other programs (e.g., universal influenza, pneumococcal vaccine programs beginning at age 60), zoster vaccine should be introduced at 60 years of age. An alternative option is initiation of zoster programs at 65 years of age, especially in jurisdictions where this age is the point of entry into influenza and pneumococcal immunization programs. A single dose of zoster vaccine is recommended at this time; the need for booster doses in the future is unknown. The vaccine may be given at the same time as trivalent seasonal influenza vaccine and polysaccharide pneumococcal vaccines.

Based on the review conducted of available economic analyses, an organized zoster immunization program may be cost-effective for adults aged 60 to 69 years and for prevention of PHN. Cost effectiveness is reduced at ages older than 69 years because of lower efficacy against zoster incidence with the current vaccine (71, 84). Cost effectiveness is improved with lower vaccine costs.

Several barriers exist to implementation of public health programs with the current vaccine. While the vaccine may be cost effective for 60-69 year olds, a catch-up program across this age span may not be deemed affordable in most or all Canadian jurisdictions, leading to inequity in the offering of publicly funded vaccine. Other barriers include supply interruptions in recent years and freezer temperature transport and storage. The availability and/or cost of this infrastructure in Canada has not been assessed, and may vary by jurisdiction and provider type. As well, potential novel solutions such as direct shipping from manufacturer to immunization service providers with new establishment of mechanisms for

verification of receipt to allow for payment from a public funding mechanism may be considered. A refrigerator-stable formulation was approved for use in Canada in late 2011; it is currently projected that this formulation will be available in Canada starting March 2014 (77). In the absence of a publicly funded program the vaccine is available for private purchase, as prescribed by health care providers.

There are no national goals for zoster prevention in Canada and development of such goals would guide planning of organized programs.

Individuals with a prior history of zoster need not be excluded from offering of zoster vaccine.

A nationally coordinated structure for evaluation of zoster vaccine programs in Canada is desirable. No means exist for assessment of incidence or burden from zoster or PHN at this time. The potential for use of administrative data exists, but other mechanisms such as sentinel surveillance could also be explored, after an evaluation of value of information from such research.

APPENDIX 1: STUDY CHARACTERISTICS AND INCREMENTAL COST-EFFECTIVENESS RATIOS (85)

Study	Country	Type of Model	Perspective	Time Frame/ Analytic Horizon	Cost[11] Per QALY Gained (by age if reported)	Currency/ year	012 CAD/QALY	Funding Source
Annemans 2010 (95)	Belgium	Markov	TPP; HC; Societal[12]	One dose/ lifetime	Costs were reported by age as well as perspective: (TPP/ Healthcare/ Societal) >=50 (6614/6966/6812) >=60 (6799/7168/7137) >=65 (7173/7575/7566) 60-64 (5686/5953/5858) 65-69 (5404/5647/5620) 60-69 (5545/5800/5739)	€ 2007	(TPP/ Healthcare/ Societal) >=50 (11034/11622/11360) >=60 (11343/11959/11907) >=65 (11967/12638/12623) 60-64 (9486/9932/9773) 65-69 (9016/9421/9376) 60-69 (9251/9676/8974)	Sanofi Pasteur

[11] In local currency as reported in the original article.
[12] TPP= third party payer; HC= healthcare. Third-party payer and healthcare perspectives may differ in European countries because the national insurer (TPP) requires a co-payment by the patient. The societal perspective incorporates lost productivity through time off work.

Bilcke 2012 (96)	Belgium	Deterministic compart-mental static cohort model	TPP	One dose/ lifetime	A sensitivity analysis varied parameters creating a "best case" and "worst case" scenario. Cost per QALY gained: (best case/worst case) 60-69: 444/45,160 70-69: 1580/69,689 80-84: 3380/128,003 85-89: 4927/297,141	€ (year not stated)[13]	Cost per QALY gained: (best case/worst case) 60-69: 633/64446 70-79: 2254/99451 80-84: 4823/182670 85-89: 11730/424042	Government funders; one author acknowledged indirect support from Pfizer
Brisson 2008 (29)	Canada	Cohort Model	N/A	N/A	Cost per QALY was not estimated.	N/A	N/A	Merck Frosst; Glaxo SmithKline
Edmunds 2001 (97)	England and Wales	Decision-analytic (cohort?)	TPP	One dose/ lifetime	Cost per QALY gained varied by the assumption made about waning. At age 65: Lifelong Efficacy: 3560 10 year efficacy: 8684 2.5 year efficacy: 27,255 C/E increases with age	£ 1998	Cost per QALY gained at age 65: Lifelong Efficacy: 11705 10 year efficacy: 28552 2.5 year efficacy: 89614	UK Medical Research Council

[13] The currency year was not stated, so 2010 was assumed based on year of publication.

Hornberger 2006 (98)	USA	Markov	Societal	One dose/ lifetime	For 60+: At a vaccine price of $100, C/E varies from 83,125/QALY if vaccine wanes after 3 years, to 28,750/QALY if protection lasts more than 30 years. At 20 years, C/E is 40,000/QALY	USD 2006	For 60+: At a vaccine price of $100, C/E varies from 114399 /QALY if vaccine wanes after 3 years, to 39566 /QALY if protection lasts more than 30 years. At 20 years, C/E is 55049/QALY	None stated
Moore 2010 (83)	UK	Markov	TPP and societal	One dose/ lifetime	Cost per QALY was reported by perspective and age. (TPP/Societal)[14] 50-54: 13,272/9,187 55-59: 11,904/8919 60-64: 10,984/9465 65-69: 10,275/10,033 70-74: 13,105 75-79: 14,972 80-84: 19,992 85-89: 33,692 90-94: 49,672 95-99: 73,978 >100: 103,082	£ 2006	(TPP/Societal) 50-54: 30980/21444 55-59: 27787 /20819 60-64: 25639/22093 65-69: 23984/23419 70-74: 30590 75-79: 34948 80-84: 46666 85-89: 78646 90-94: 115947 95-99: 172684 >100: 240620	Two authors employed by Sanofi Pasteur MSD

[14] Societal and TPP become identical at age 70 because Moore assumed no one aged 70 or over was in the workforce.

Najafzadeh 2009 (84)	Canada	Markov (discrete event)	TPP	One dose/ lifetime	Cost per QALY: >60: 41,709 60-74: 35,357 >75: 64,996	CAD 2008	Cost per QALY: >60: 44370 60-74: 37613 >75: 69143	None stated
Pellissier 2007 (102)	USA	Markov	TPP; societal	One dose/ lifetime	Cost per QALY was reported by perspective and calculated specifically for immunocompetent individuals. All 60+: TPP: 18, 439 Societal: 16,229 Immunocompetent: TPP: 27,609 Societal: 25,379	USD 2006	All 60+: TPP: 23,242 Societal: 20,457 Immuno-competent: TPP: 34,801 Societal: 31,990	Merck Frosst
Rothberg 2007 (101)	USA	Markov	Societal	One dose/ lifetime	Cost per QALY was reported by age and sex. Males: 60+: 143,721 70+: 66,055 80+: 191, 364 Female: 60+: 89,566 70+: 43,650 80+: 123,484	USD 2005	Males: 60+: 197,794 70+: 90,907 80+: 263,362 Female: 60+: 123,263 70+: 60,073 80+: 169,943	None stated

Szucs 2011 (99)	Switzerland	Markov	TPP; societal	One dose/ lifetime	Cost per QALY was reported by perspective and age. TPP/Society: 60-69: 18,089/19,998 70-79: 25,538/28,544 65+: 26,083/29,104 70+: 30,934/34,543	CHF (yr?)[15]	TPP/Society: 60-69: 18,241/20,166 70-79: 25,753/28,784 65+: 26,302/29,349 70+: 31,194/34,833	Two authors employed by SPMSD; funded by SPMSD
Van Hoek 2009 (100)	UK	Markov	TPP	One dose/ lifetime	Cost per QALY was reported by age. 60: 26,705 65: 20,412 70: 15,146 75: 18,546	£ 2006	60: 62,337 65: 47,647 70: 35,355 75: 43,291	Government funders (EU POLY-MOD program and UK Dept of Health)

[15] The year of the currency was not stated; 2006 was assumed based on Szucs et al, 2013.

Van Lier 2010 (91)	Netherlands	Markov	Societal	One dose/ lifetime	Cost per QALY gained was reported for HZ alone, and for HZ assuming the vaccine also reduced QALY decrements associated with PHN. HZ/HZ+PHN 60+: 38,519 65+: 31,228 70+: 21,716/9861 75+: 24,336/9959 80+: 34,449/10,552	€ 2008	HZ/HZ+PHN 60+: 62,801 65+: 50,914 70+: 35,405/16,077 75+: 24,336/16,237 80+: 56,165/17,204	None stated

APPENDIX 2: EPIDEMIOLOGICAL ASSUMPTIONS AND DATA SOURCES (85)

Study	Data Sources	Vaccine Efficacy Source	Vaccine Coverage	Duration of Protection	QALY Source
Annemans 2010 (95)	Incidence of HZ: Belgian Sentinel of General Practitioners Proportion of HZ that develop PHN: GPRD (89) Length and severity of PHN: SPS	SPS	20%	Lifelong (waning considered in sensitivity analysis)	Oster 2005 (121)
Bilcke 2012 (96)	HZ incidence: Belgium Sentinel of General Practitioners demographic data: national statistics average from 1990-2007 length and severity of PHN: SPS	SPS	30%	Considered during sensitivity analysis	Scott 2003 (122)
Brisson 2008 (29)	HZ incidence: MB physician claims Hosp. data: CIHI Morbidity database	SPS	N/A	Lifelong; waning considered during sensitivity analysis (8.3% in worst case)	Two Canadian multi-center studies (6 mo. Duration)
Edmunds 2001 (97)	Age-specific HZ incidence: prospective study in general practice and from two sentinel surveillance systems Proportion that develop PHN: prospective study and one sentinel system mortality data: taken from Office of National Statistics (1998)	Unknown – uses a variety of estimates	60%	2.5 years to lifelong	Bala 1998 (Standard gambles; n=114, age = 65-70) (123)

Hornberger 2006 (98)	HZ incidence: SPS Clinically relevant pain: SPS	SPS	100%	Durations ranging from 3-30 years	Coplan 2004 – fitted from SPS (22)
Moore 2010 (83)	HZ incidence: GPRD (89) Proportion that develop PHN: SPS Hospitalization: Edmunds 2001 (97) demographics and mortality from national government statistics	SPS	40%	Lifetime (waning considered in sensitivity analysis)	Oster 2005 (121)
Najafzadeh 2009 (84)	HZ incidence: SPS Proportion developing PHN: SPS Demographics and mortality rates: Statistics Canada Hospitalization data: BC admin data	SPS	100%	Wane function of 15 years in base case	Oster 2005 (121)
Pellissier 2007 (102)	mortality data: CDC HZ incidence: Medstat Marketscan database Proportion developing PHN: SPS Non-pain complications: admin data from Olmsted County, MN	SPS	100%?	Lifetime in base case	Oster 2005 (121); Bala 1998 (123)
Rothberg 2007 (101)	HZ incidence: USA administrative database (124) Proportion developing PHN: SPS Non-pain complications: variety of published studies	SPS	100%	Waning function; 10 years at base	Oster 2005 (121)

Szucs 2011 (99)	HZ incidence: Swiss sentinel surveillance, Proportion developing PHN: GPRD (89) Demographic data: national stats Hospitalization: literature	SPS	20%	Lifetime	Oster 2005 (121)
Van Hoek 2009 (100)	HZ incidence: GPRD and other UK admin databases Proportion developing PHN: SPS Mortality: vital statistics	SPS	73.5%	Waning function estimated from SPS	Coplan 2004 (22)
Van Lier 2010 (91)	Incidence data: Netherlands information Network of General Practice Proportion that develop PHN: SPS; Did not assume a fixed proportion developing PHN but rather estimated number with clinically relevant pain Much of the rest is based on Van Hoek (100)	SPS	75%	age-dependent 7.5 years in base case	Based on Van Hoek (100)

APPENDIX 3: COSTING ASSUMPTIONS AND DATA SOURCES (85)

Study	Currency/ Year	Vaccine Cost[16]	Vaccine Cost (2012 CAD)[17]	Healthcare Costs	Productivity Costs	Discount Rate(s)
Annemans 2010 (95)	€ 2007	141.18	236	Used a Burden of Illness study based on expert opinion; costs are based on standard administration data sources	Included for those aged <70; based on Belgian labour market data	3% costs/1.5% outcomes
Bilcke 2012 (96)	€ (year not stated)	90+21.53	159	Ambulatory and Hospitalization costs by age Direct costs are estimated based on survey data	N/A	3% costs/1.5% outcomes
Brisson 2008 (29)	N/A	N/A		N/A	N/A	N/A
Edmunds 2001 (97)	£ 1998	80	263	Cost per weighted case; condition-specific estimates NHS Financial Manual	N/A	3%
Hornberger 2006 (98)	USD 2006	50	69	Diagnostically Related Group (DRG) estimation of hospital costs; updated estimates in the literature with contemporary sources; assumed 2 Physician visits per case	Sources USA Dept. of Labor Statistics	3%
Moore 2010 (83)	£ 2006	95+10.40	246	Based on GPRD and reported in Gauthier (89) Varies by the severity of pain, not age	Source: national labour market statistics and Gauthier (89)	3.5%

[16] Some studies included a separate cost of administration. This is presented as a second figure (i.e. vaccine cost + administration cost).
[17] Only the vaccine cost is presented in Canadian dollars because this is an important input parameter and responsible for variations in cost per QALY. The cost of administration is not included.

Najafzadeh 2009 (84)	CAD 2008	150	160	Based on BC medical services plan	N/A	5%
Pellissier 2007 (102)	USD 2006	150+18	212	Medstat database	Self-administered questionnaire	3%
Rothberg 2007 (101)	USD 2005	145.35+ 3.49	205	Literature: Based on Grant (125) Updated with a national cost-to-charge database	Literature: Based on Scott (126)	3%
Szucs 2011 (99)	CHF (yr?)	240.7+ 25.2	268	Expert Opinion	Expert Opinion	3.5% for costs/1.5% for outcomes
Van Hoek 2009 (100)	£ 2006	55+10	152	GPRD	N/A	3.5%
Van Lier 2010 (91)	€ 2008	110/77[18]	179/126	Literature: based on van Wijck (127)	Literature: Based on Scott (126)	4% costs/1.5% outcomes

[18] These two costs represent two different assumptions about vaccine price. Van Lier considered both.

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