



Summary of the NACI Update on Herpes Zoster Vaccines

R Warrington^{1,2}, S Ismail³ on behalf of the National Advisory Committee on Immunization (NACI)*

Abstract

Background: Steep increases in herpes zoster (HZ) incidence, hospitalization due to HZ and the risk of post-herpetic neuralgia as a complication of HZ occur in people over 50 years of age. Two HZ vaccines are currently authorized for use in those 50 years of age and older in Canada: a live attenuated zoster vaccine (LZV) authorized in 2008; and a recombinant subunit vaccine (RZV) authorized in October 2017.

Objectives: To review current evidence and develop guidance on whether the previously authorized LZV (Zostavax[®]) and/or the recently authorized RZV (Shingrix[®]) vaccine should be offered to Canadians 50 years of age and older: 1) at a population-level, in publicly funded immunization programs; and 2) at an individual-level, to individuals wishing to prevent HZ, or by clinicians wishing to advise individual patients about preventing HZ.

Methods: The National Advisory Committee on Immunization (NACI) Herpes Zoster Working Group developed a predefined search strategy to identify all eligible studies, assessed their quality, and summarized and analyzed the findings. A Cost Utility Analysis of LZV and RZV was also conducted from a health care system perspective. Recommendations were proposed according to NACI's evidence-based process. The strength of these recommendations was defined, and the Grade of evidence supporting them was identified. In light of the evidence, the recommendations were then considered and approved by NACI.

Results: Five recommendations were developed for public health and individual-level decision-making. 1) RZV *should be offered* to populations/individuals ≥ 50 years of age without contraindications (Strong NACI Recommendation, Grade A evidence). 2) RZV *should be offered* to populations/individuals ≥ 50 years of age without contraindications who have previously been vaccinated with LZV (Strong NACI Recommendation, Grade A evidence). Re-immunization with two doses of RZV may be considered one year after LZV (Discretionary NACI Recommendation, Grade I evidence). 3) RZV *should be offered* to populations/individuals ≥ 50 years of age without contraindications who have had a previous episode of HZ (Strong NACI Recommendation, Grade B evidence). Immunization with two doses of RZV may be considered one year after the HZ episode (Discretionary NACI Recommendation, Grade I evidence). 4) LZV *may be considered* for immunocompetent populations/individuals ≥ 50 years of age without contraindications when RZV vaccine is contraindicated, unavailable or inaccessible (Discretionary NACI Recommendation, Grade A evidence). 5) RZV vaccine (not LZV) *may be considered* in immunocompromised adults ≥ 50 years of age on a case-by-case basis (Discretionary NACI Recommendation, Grade I evidence).

Conclusion: Both vaccines have been shown to be safe and immunogenic and to reduce the incidence of HZ and post-herpetic neuralgia. Vaccine efficacy of LZV against HZ decreases with age at, and time since vaccination. The vaccine efficacy of RZV remains higher and appears to decline more slowly than vaccine efficacy of LZV across all age groups. Both vaccines are cost-effective in those 50 years of age and older compared with no vaccination, especially in those 65–79 years of age. RZV is more cost-effective than LZV.

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Introduction

Herpes zoster (HZ), or shingles, is characterized by neuropathic pain and dermatomal vesicular rash. It results from reactivation of varicella zoster virus (VZV), which occurs with reduced cellular immune response associated with aging or immune suppression.

The most frequent and often debilitating complication of HZ is post-herpetic neuralgia. Nearly one in three Canadians develops HZ during their lifetime (1). Age is the predominant risk factor for the development of HZ, as well as post-herpetic neuralgia and

Affiliations

¹ NACI Herpes Zoster Working Group Chair, Edmonton, AB

² Department of Internal Medicine, Adult Allergy & Clinical Immunology, University of Manitoba, Winnipeg, MB

³ Centre for Immunization and Respiratory Infectious Diseases, Public Health Agency of Canada, Ottawa, ON

*Correspondence: phac.naci-ccni.aspc@canada.ca



hospitalization among HZ cases, with steep increases occurring over 50 years of age (2–7). Peak hospitalization rates for HZ and post-herpetic neuralgia risk per HZ case are observed among those 65 years of age and older (1,4,7–9).

In Canada in 2008, a live attenuated vaccine against HZ (LZV, Zostavax®) was approved for use among those 60 years of age and older, and in 2011 it was approved for use in those 50 years of age and older. In 2010 and 2014, Canada's National Advisory Committee on Immunization (NACI) published evidence-based recommendations on the use of LZV in immunocompetent individuals 60 years of age and older (10,11). NACI also recommended that LZV *may be used* in patients 50–59 years of age because, while it was shown to be safe and efficacious in this age group, the duration of protection from the vaccine was unknown beyond five years, and it was uncertain whether protection would persist at older ages when the burden of HZ is greatest. In May 2014, the Canadian Immunization Committee recommended that LZV be routinely offered to immunocompetent adults aged 60–65 years of age without contraindications on the basis of the epidemiology of VZV, vaccine characteristics, disease modeling and economic analysis, as well as on the feasibility and acceptability of immunization programs for HZ (12). While LZV has been available for private purchase, no publicly-funded immunization program has been offered in Canada until Ontario offered the vaccine to individuals 65–70 years of age in September 2016 (13).

In October 2017, Canada was the first country to authorize the use of a recombinant subunit HZ vaccine (RZV, Shingrix®) containing VZV glycoprotein E and the novel ASO1_B adjuvant system. This triggered the need for an updated NACI Advisory Committee Statement on the Use of Herpes Zoster Vaccines. The primary objective of this statement is to review current evidence and develop guidance on the use of RZV, as well as whether the previously authorized LZV and/or the recently authorized RZV vaccine should be offered to Canadians ≥50 years of age at a population-level, in publicly-funded immunization programs and at an individual-level, to individuals wishing to prevent HZ or by clinicians wishing to advise individual patients about preventing HZ, with vaccines that may not currently be included in public health immunization programs. Complete details can be found in the *National Advisory Committee on Immunization Update on the Use of Herpes Zoster Vaccines* (14). The objective of this article is to summarize the main findings of the update.

Methods

The NACI Herpes Zoster Working Group (HZWG) performed literature reviews and reviewed vaccine manufacturer-provided data on the topic of HZ and HZ vaccines. All evidence was rated, critically appraised and reported in evidence tables. Studies on RZV vaccine immunogenicity, safety and efficacy in various immunocompromised groups ≥18 years of age with various dosing schedules were ongoing at the time of NACI deliberations; therefore, they were not included for this review.

The NACI will monitor and review the evolving evidence on HZ vaccines in those who are immunocompromised in a separate advisory committee statement.

A knowledge synthesis was performed, the evidence was critically appraised and the HZWG proposed specific evidence-based recommendations according to NACI's evidence-based process for developing recommendations (15). This included elucidating the rationale and relevant considerations. New terminology has recently been developed to define the strength of NACI Recommendations:

- A *strong recommendation* applies to most populations/individuals and should be followed unless a clear and compelling rationale for an alternative approach is present.
- A *discretionary recommendation* may be considered for some populations/individuals in some circumstances. Alternative approaches may be reasonable.

Results

Both LZV and RZV have been shown to be safe, immunogenic and effective in reducing the incidence of HZ and its complications, such as post-herpetic neuralgia. With LZV, vaccine efficacy against HZ decreases with age at, and time since, vaccination. The vaccine efficacy of RZV remains higher and appears to decline more slowly than vaccine efficacy of LZV across all age groups. The RZV vaccine efficacy against incident HZ and post-herpetic neuralgia in the three years after immunization appears to be double that observed for LZV. Significant waning of protection has been observed one year after immunization with LZV. In contrast, vaccine efficacy of RZV against incident HZ in the four years post-immunization remains consistent, with no significant decreases observed over time. LZV is significantly less effective in adults over 70 years of age compared with adults 50–59 years of age, whereas differences in four year vaccine efficacy of RZV against HZ are non-significant across different age groups. RZV is more reactogenic than LZV due to the adjuvant in RZV, which induces a high cellular immune response to help address the natural age-related decline in immunity. While both vaccines are cost-effective in those 50 years of age and older compared with no vaccination especially in those 65–79 years of age, RZV is more cost-effective than LZV from a health care system perspective. The review of the literature on the use of HZ vaccines and current HZ vaccine recommendations are published in the full NACI statement update (14) and the HZ chapter of the *Canadian Immunization Guide* (16).

Recommendations and rationale

The NACI approved five recommendations for public health level and individual level decision-making with the following rationales.

1. **RZV should be offered to populations/individuals ≥50 years of age without contraindications (Strong NACI Recommendation, Grade A evidence).**

Both LZV and RZV are safe, immunogenic and effective in preventing HZ and post-herpetic neuralgia. On the balance, NACI felt that the higher efficacy of the RZV vaccine in adults 50 years of age and older, minimal waning of protection and cost-effectiveness supports a public health program level recommendation to vaccinate populations ≥50 years of age, who are at higher risk of HZ and post-herpetic neuralgia and will likely continue to be protected with RZV at older ages as the risk of HZ and post-herpetic neuralgia continues to increase. From a



public health program level perspective, RZV has been shown to be more cost effective than LZV. Programs will require strategies (e.g., education, recalls/reminders) to ensure adherence to the two dose schedule for RZV (as vaccine efficacy and duration of protection is unclear after only one dose), and provide counseling on short term reactogenicity of the vaccine. If, due to operational constraints, prioritization of targeted immunization programs is required for implementation, jurisdictions may wish to consider the relative merits of vaccinating different age cohorts (with respect to epidemiology and cost-effectiveness). From an individual level perspective, individuals wishing to prevent HZ or clinicians wishing to advise patients may consider the individual cost of RZV vs LZV vaccines. Individuals should be prepared to adhere to a two dose schedule for the RZV vaccine (as vaccine efficacy and duration of protection is unknown after only one dose) and to understand that they may experience more short term reactogenicity from the RZV vaccine.

2. RZV should be offered to populations/individuals ≥ 50 years of age without contraindications who have previously been vaccinated with LZV (Strong NACI Recommendation, Grade A evidence).

2a. Re-immunization with two doses of RZV may be considered one year after LZV (Discretionary NACI Recommendation, Grade I evidence).

Prior recipients of LZV vaccine will derive additional protection from completion of the two dose series of RZV given higher and more durable vaccine efficacy across age groups. Comparable safety, reactogenicity and immunogenicity have been demonstrated between those who have previously been vaccinated with LZV and those who have not. For those who have previously been vaccinated with LZV, consideration of the interval between LZV and RZV vaccination will depend on age of vaccination with LZV (since vaccine efficacy decreases with age), as well as time since LZV vaccination (since efficacy wanes after the first year). Based on limited evidence, NACI suggests re-immunization with two doses of RZV after one year post-LZV administration due to rapidly declining LZV effectiveness after the first year post-vaccination. While the only published study to date investigating immunization with RZV following LZV used an interval of at least five years, there is no reason to believe that a shorter interval would be harmful.

3. RZV should be offered to populations/individuals ≥ 50 years of age without contraindications who have had a previous episode of HZ (Strong NACI Recommendation, Grade B evidence).

3a. Immunization with two doses of RZV may be considered one year after the HZ episode (Discretionary NACI Recommendation, Grade I evidence).

Similar to its 2014 recommendation for LZV, NACI recommends immunization with RZV in individuals with a prior episode of HZ. Individuals with a prior episode of HZ are still at risk of HZ, and a history of HZ is unreliable; therefore, vaccination with RZV in those who report a prior history of HZ will be beneficial. Furthermore, one study has shown no differences in safety or immunogenicity of RZV in individuals with a prior episode of HZ. In the absence of evidence on an appropriate interval, NACI maintains its previous suggestion of waiting at least one year post HZ episode prior to the administration of herpes zoster vaccine.

4. LZV may be considered for immunocompetent populations/individuals ≥ 50 years of age without contraindications when RZV vaccine is contraindicated, unavailable or inaccessible (Discretionary NACI Recommendation, Grade A evidence).

The NACI concludes (as it has in previous HZ advisory committee statements) that there is good evidence to recommend immunization with LZV in adults aged ≥ 60 years (Grade A evidence). However, the recommendation on the use of this vaccine in immunocompetent populations ≥ 60 years of age is now "Discretionary" due to the comparative evidence on higher efficacy, longer duration of protection, and relative cost effectiveness of the newly authorized RZV vaccine. Although LZV is safe and efficacious in 50–59 year olds and was previously recommended by NACI on a discretionary basis for this age group, waning protection of the vaccine means that it may not provide optimal ongoing protection at older ages where the risk of HZ and post-herpetic neuralgia is greatest. With the newly authorized RZV vaccine and its higher efficacy and longer duration of protection in this age group, NACI now strongly recommends that RZV be used in adults 50–59 years in addition to adults ≥ 60 years, without contraindications. LZV vaccine may still be considered in individuals in whom RZV vaccine is contraindicated (i.e., known hypersensitivity to any component of the vaccine), or if RZV is not available or inaccessible due to cost. LZV has been authorized in Canada since 2008 and has been shown to be safe, immunogenic and effective.

5. RZV vaccine (not LZV) may be considered in immunocompromised adults ≥ 50 years of age on a case by case basis (Discretionary NACI Recommendation, Grade I evidence).

Unlike with LZV, immunocompromise is not a contraindication for RZV. Based on the burden of illness of HZ in immunocompromised individuals and general guidance on the use of inactivated vaccines versus live vaccines in those who are immunocompromised, NACI feels that the benefits of considering vaccination with RZV (instead of LZV) in immunocompromised individuals on a case by case basis outweighs the risks at this time. NACI will monitor the evidence as it evolves and will reassess individual level and public health program level recommendations in different immunocompromised individuals and populations ≥ 18 years of age as soon as the evidence from ongoing trials becomes available.

Table 1 provides a summary of NACI's updated recommendations on the use of LZV and RZV for public health program level decision-making that is applicable to provincial and territorial authorities who are making decisions for publicly funded immunization programs. The strength of each recommendation and the grading of the body of evidence supporting the recommendation are included.

Table 2 provides a summary of NACI's updated recommendations on the use of LZV and RZV for individual level decision-making that is applicable to individuals wishing to prevent HZ, or clinicians wishing to advise individual patients about preventing HZ with vaccines that may not currently be included in public health immunization programs. The strength of each recommendation and the grading of the body of evidence supporting the recommendation is included.



Table 1: Summary of 2018 NACI recommendations on the use of herpes zoster vaccines for public health program level decision-making^a

Vaccine type	NACI Recommendation (Strength of recommendation)	Grade of evidence supporting recommendation
RZV	1. NACI recommends that RZV should be offered to populations ≥50 years of age without contraindications. (Strong NACI Recommendation)	NACI concludes that there is good evidence to recommend immunization. (Grade A evidence)
	2. NACI recommends that RZV should be offered to populations ≥50 years of age without contraindications who have previously been vaccinated with LZV. (Strong NACI Recommendation)	NACI concludes that there is good evidence to recommend immunization. (Grade A evidence)
	2a. NACI recommends that for adults ≥50 years of age who have previously been immunized with LZV, re-immunization with two doses of RZV may be considered one year after LZV. (Discretionary NACI Recommendation; based on expert opinion)	NACI concludes that there is insufficient evidence to recommend an interval between LZV and RZV. (Grade I evidence)
	3. NACI recommends that RZV should be offered to populations ≥50 years of age without contraindications who have had a previous episode of HZ. (Strong NACI Recommendation)	NACI concludes that there is fair evidence to recommend immunization. (Grade B evidence)
	3a. NACI recommends that for adults ≥50 years of age who have had a previous episode of HZ, immunization with two doses of RZV may be considered at least one year after the HZ episode. (Discretionary NACI Recommendation; based on expert opinion)	NACI concludes that there is insufficient evidence to recommend an interval between a previous episode of HZ and vaccination with RZV. (Grade I evidence)
LZV	4. NACI recommends that LZV <i>may be considered</i> for immunocompetent populations ≥50 years of age without contraindications when RZV is contraindicated or unavailable. (Discretionary NACI Recommendation)	NACI concludes that there is good evidence to recommend (Grade A evidence)
RZV vs LZV in immunocompromised populations	5. NACI recommends that RZV (not LZV) <i>may be considered</i> in immunocompromised adults ≥50 years of age on a case by case basis. (Discretionary NACI Recommendation; based on expert opinion) NACI will review the evidence as it evolves and reassess recommendations.	NACI concludes that there is insufficient evidence at this time to recommend immunization. (Grade I evidence)

Abbreviations: HZ, herpes zoster; NACI, National Advisory Committee on Immunization; LZV, live attenuated zoster vaccine; RZV, recombinant subunit vaccine
^a In considering these recommendations, provinces and territories may take into account other local operational factors (e.g. current immunization programs, resources), and may wish to review differences between age cohorts (e.g., with respect to epidemiology and cost-effectiveness) outlined in the 2018 NACI Statement if prioritization of targeted immunization programs is required for implementation

Table 2: Summary of 2018 NACI recommendations on the use of herpes zoster vaccines for individual level decision-making^a

Vaccine type	NACI Recommendation (Strength of recommendation)	Grade of evidence supporting recommendation
RZV	1. NACI recommends that RZV <i>should be</i> offered to individuals ≥50 years of age without contraindications. (Strong NACI Recommendation)	NACI concludes that there is good evidence to recommend immunization. (Grade A evidence)
	2. NACI recommends that RZV <i>should be</i> offered to individuals ≥50 years of age without contraindications who have previously been vaccinated with LZV. (Strong NACI Recommendation)	NACI concludes that there is good evidence to recommend immunization. (Grade A evidence)
	2a. NACI recommends that for adults ≥50 years of age who have previously been immunized with LZV, re-immunization with two doses of RZV may be considered one year after LZV. (Discretionary NACI Recommendation; based on expert opinion)	NACI concludes that there is insufficient evidence to recommend an interval between LZV and RZV. (Grade I evidence)
	3. NACI recommends that RZV <i>should be</i> offered to individuals ≥50 years of age without contraindications who have had a previous episode of HZ. (Strong NACI Recommendation)	NACI concludes that there is fair evidence to recommend immunization. (Grade B evidence)
	3a. NACI recommends that for adults ≥50 years of age who have had a previous episode of HZ, immunization with two doses of RZV may be considered one year after the HZ episode. (Discretionary NACI Recommendation; based on expert opinion)	NACI concludes that there is insufficient evidence to recommend an interval between a previous episode of HZ and vaccination with RZV. (Grade I evidence).
LZV	4. NACI recommends that LZV <i>may be considered</i> for immunocompetent individuals ≥50 years of age without contraindications when RZV is contraindicated, unavailable, or inaccessible. (Discretionary NACI Recommendation)	NACI concludes that there is good evidence to recommend immunization. (Grade A evidence)
RZV vs LZV in immunocompromised populations	5. NACI recommends that RZV (not LZV) <i>may be considered</i> in immunocompromised adults ≥50 years of age on a case by case basis. (Discretionary NACI Recommendation; based on expert opinion) NACI will review the evidence as it evolves and reassess recommendations.	NACI concludes that there is insufficient evidence at this time to recommend immunization (Grade I evidence)

Abbreviations: HZ, herpes zoster; NACI, National Advisory Committee on Immunization; LZV, live attenuated zoster vaccine; RZV, recombinant subunit vaccine
^a In considering these recommendations, individuals/clinicians may wish to review the decision points with respect to vaccine and age at vaccination outlined in the 2018 NACI Statement



Conclusion

The NACI has concluded that both the RZV and LZV vaccines are safe, immunogenic and cost-effective and reduce the incidence of HZ and post-herpetic neuralgia; however, while vaccine efficacy of LZV decreases with age at, and time since, vaccination, vaccine efficacy of RZV remains higher and appears to decline more slowly than vaccine efficacy of LZV across all age groups. RZV vaccine efficacy against incident HZ and post-herpetic neuralgia in the three years post-immunization appears to be double that observed for LZV. RZV vaccine efficacy against incident HZ in the four years post-immunization remains consistent, with no significant decreases observed over time; in contrast, significant waning of protection has been observed one-year post-immunization with LZV. Differences in RZV four-year vaccine efficacy against incident HZ are non-significant across different age groups; in contrast, LZV is significantly less effective in adults over 70 years of age compared with adults 50–59 years of age. Due to the adjuvant in RZV, which induces a high cellular immune response to help address the natural age-related decline in immunity, this vaccine is more reactogenic than LZV. However, this reactogenicity is transient, and education to improve adherence to the second dose of the RZV vaccination schedule will be important.

Both vaccines are cost-effective in those 50 years of age and older compared with no vaccination, especially in those 65–79 years of age because of the increased burden of illness with age (increased risk of hospitalization and post-herpetic neuralgia per HZ case especially in those 65 years of age and older) and the likelihood that the vaccine will be effective during the years when burden of illness is high (unless vaccine efficacy wanes quickly). In addition, the benefits of vaccination accrue over a longer period of time due to the longer life expectancy in this age cohort compared to those 80 years of age and older. From a public health perspective, the HZ vaccine may be simultaneously administered with other adult vaccines to improve coverage and reduce operational costs. For all age cohorts considered, RZV is more cost-effective than LZV.

Based on the evidence reviewed, NACI recommends immunization against herpes zoster.

Authors' statement

RW – Writing original summary draft – review and editing
SI – Writing original summary draft – review and editing

This is a summary of the NACI Herpes Zoster Statement, which was prepared by S Ismail, M Tunis, O Baclic, K Eng, MK Doll, J Hu, S Duchesne-Belanger, R Warrington and was approved by NACI.

Conflict of interest

None.

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Herpes Zoster Working Group Members: R Warrington (Chair), S Deeks, P De Wals, K Dooling, K Eng, J Gallivan, S Ismail, M Landry, C Rotstein, C Sauvageau, SE Straus, M Tunis

NACI Members: C Quach (Chair), W Vaudry (Vice-Chair), N Dayneka, S Deeks, P DeWals, V Dubey, R Harrison, M Lavoie, M Salvadori, B Sander, C Rotstein, N Sicard, R Warrington

Liaison Representatives: J Brophy (Canadian Association for Immunization Research and Evaluation), E Castillo (Society of Obstetricians and Gynaecologists of Canada), A Cohn (Centers for Disease Control and Prevention, United States), T Cole (Canadian Immunization Committee), J Emili (College of Family Physicians of Canada), C Mah (Canadian Public Health Association), D Moore (Canadian Paediatric Society), A Pham-Huy (Association of Medical Microbiology and Infectious Disease Canada)

Ex-Officio Representatives: K Barnes (National Defence and the Canadian Armed Forces), G Charos (Centre for Immunization and Respiratory Infectious Diseases [CIRID], Public Health Agency of Canada [PHAC]), J Gallivan (Marketed Health Products Directorate, HC), J Pennock (CIRID, PHAC), R Pless (Biologics and Genetic Therapies Directorate, Health Canada [HC]), T Wong (First Nations and Inuit Health Branch, HC)

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