Update on herpes zoster vaccination

A family practitioner's guide

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Abstract

Objective To answer frequently asked questions surrounding the use of the new herpes zoster (HZ) vaccine.

Sources of information Published results of clinical trials and other studies, recommendations from the Canadian National Advisory Committee on Immunization, and the US Advisory Committee on Immunization Practices; data were also obtained from the vaccine's Health Canada–approved product monograph.

Main message Herpes zoster results from reactivation of the varicella-zoster virus; postherpetic neuralgia (PHN) is its most common and serious complication. The incidence of PHN after HZ is directly related to age, with 50% of affected individuals older than 60 years experiencing persistent and unrelieved pain. The live virus HZ vaccine reduces the incidence of HZ by about 50% and the occurrence of PHN by two-thirds, with vaccinated individuals experiencing attenuated or shortened symptoms. The vaccine is contraindicated in many immunocompromised patients and might not be effective in patients taking antiviral medications active against the HZ virus. Physicians should be aware of the different recommendations for these groups.

Conclusion The HZ vaccine is a safe and effective preventive measure for reducing the overall burden and severity of HZ in older adults. The vaccine appears to be cost-effective when administered to adults aged 60 years and older.

KEY POINTS The greatest benefit of the herpes zoster (HZ) vaccine is its prevention of postherpetic neuralgia, which can be extremely difficult to treat. Clinical trials have demonstrated the efficacy of the vaccine. This live virus vaccine is contraindicated in many immunocompromised individuals. Those taking antiviral medications against the HZ virus should cease treatment at least 24 hours before administration of the vaccine and avoid restarting treatment for at least 2 weeks after. Side effects typically involve injection site reactions (eg, erythema, pain, pruritus). Delivering the HZ vaccine is complicated because the vaccine must be stored frozen, it is costly, and it is not publicly funded in Canada. However, the burden of HZ and postherpetic neuralgia is such that both the US Advisory Committee on Immunization Practices and the Canadian National Advisory Committee on Immunization recommend routine vaccination in adults 60 years of age and older.

Herpes zoster (HZ), or shingles, results from reactivation of the varicella-zoster virus (VZV), which lies dormant in the spinal and cranial sensory ganglia following a primary infection with varicella (chickenpox), usually during childhood. Herpes zoster is characterized by a unilateral, cutaneous, usually painful vesicular rash that typically presents in a single dermatome. Complications of HZ can include sight-threatening infections, central nervous system infections, nerve palsies, neuromuscular disease (including Guillain-Barré syndrome), and secondary bacterial infections, to name a few.[1] However, postherpetic neuralgia (PHN) is its most common and serious complication. In Canada there are 130 000 cases of HZ and 17 000 cases of associated PHN each year.[2]

Neuralgic pain might develop before the HZ rash; in some cases, the classic HZ rash might not even appear (*zoster sine herpete*). The incidence of PHN after HZ is directly related to age.[3] Typically, 10% of those with HZ will experience persistent pain 1 month following rash onset; in those 60 years of age and older, this can increase to 50% of HZ cases, despite treatment.[4-6] Half of patients who continue to suffer after 1 year will continue to have unrelieved pain, which will inevitably affect quality of life.[7]

Postherpetic neuralgia is notoriously difficult and sometimes even impossible to treat, despite the use of strong analgesics such as opioids. Pathologic evidence suggests that VZV can cause permanent peripheral and central nervous system damage,[7] destroying sites of intrinsic pain inhibitory mechanisms where analgesics act; as a result, patients are left inadequately relieved by, or indeed refractory to, all drugs for pain. Antiviral medications, even when initiated within 72

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hours of onset, are only marginally effective for the prevention of PHN.[8]

The vaccine reduces the incidence of HZ by about 50% and the occurrence of PHN by two-thirds, with vaccinated individuals experiencing attenuated or shortened symptoms. The vaccine has few adverse effects, primarily injection site reactions.[9] It is now approved in Canada for immunocompetent adults aged 50 years of age and older.[1,10]

Sources of information

Scientific evidence supports the recommendation that patients be vaccinated. However, a number of areas of uncertainty and questions regarding the use of the vaccine remain. Particularly noteworthy are the differences between Health Canada–approved indications and the recommendations made by both the Canadian National Advisory Committee on Immunization (NACI) and the US Advisory Committee on Immunization Practices (ACIP). This review aimed to synthesize the evidence and recommendations about the HZ vaccine; the information provided was derived from published clinical studies, recommendations, and guidelines, as well as from the Zostavax (HZ vaccine marketed by Merck) product monograph.[10,*] Zostavax is the only HZ vaccine approved for use in Canada; others are still undergoing clinical testing.

Frequently asked questions

The following questions are routinely posed by practitioners regarding the use of the HZ vaccine; the answers can serve as a useful guide in family practice.

1. What is the duration of protection provided by the vaccine? The duration of protection is not currently known. In the Shingles Prevention Study (SPS), vaccine efficacy was maintained through 4 years of follow-up.[9,10] An ongoing vaccine persistence study of more than 14 000 individuals (7320 in the vaccine group, 6950 in the placebo group) will eventually provide data on degree of protection 5 to 10 years postvaccination[11]; to date, evidence suggests that protection persists for up to 7 years.[12] The need for revaccination has not yet been defined.[10]

2. What is the efficacy of this vaccine? The pivotal efficacy trial for the HZ vaccine (ie, the SPS) included more than 38 500 adults 60 years of age and older. In that study, the vaccine reduced the incidence of shingles by 51% and the incidence of persistent, severe pain after shingles (ie, PHN) by 66%.[9,13] For the average 69-year-old, the risk of shingles in the 5-year period after vaccination is expected to be reduced from 5.5% to 2.5% (from 1 in 18 to 1 in 40) and the risk of PHN from 0.7% to about 0.25% (from 1 in 140 to 1 in 400).[14]

3. Can the vaccine be given to adults aged 50 to 59 years? Yes. In May 2011 Health Canada extended the indication of the HZ vaccine to those 50 years and older based on data from a large randomized, double-blind, placebo-controlled trial of people between 50 and 59 years of age (N = 22 439). The study demonstrated that the vaccine was safe and reduced the incidence of HZ (2.0 cases per 1000 person-years vs 6.6 cases per 1000 person-years in the placebo group), with a protective efficacy against HZ of 69.8%.[10,15] Further, NACI also recommends that the HZ vaccine be used in patients 50 years of age and older.[1]

4. Will the vaccine benefit patients who have already had HZ? Having an episode of HZ has an immunizing effect, greatly reducing the probability of a second event.[16] That said, patients with a history of severe HZ are often the most insistent on receiving the vaccine,[17] and concerns have been raised about the validity of patient histories of HZ. For these reasons, both the Centers for Disease Control and Prevention and the ACIP recommend that adults be vaccinated whether or not they report a previous episode of HZ.[11]

5. Can the HZ vaccine be administered to those with an unknown history of chickenpox? Yes. An estimated 90% of Canadian adults have had a previous VZV infection. Thus, almost all adults 60 years of age or older have been infected with VZV, regardless of patient-reported history or recall. There is no need to test immunity levels before administering the vaccine. However, if a patient is known to be susceptible to VZV, it is recommended that 2 doses of the varicella vaccine be administered, at least 4 weeks apart, rather than administering the HZ vaccine.[11,18,19]

6. Can the vaccine be given concurrently with other vaccines? The HZ vaccine is a live, attenuated virus vaccine. It can be administered concurrently with all other live and inactivated vaccines, including those commonly administered to individuals 60 years of age and older.[20] The Centers for Disease Control recommend that the HZ vaccine be administered with the pneumococcal vaccine and the influenza vaccine (ie, at the same visit).[21] This recommendation differs from the NACI recommendation and is based on data from a recent observational study that found no evidence of increased risk of HZ in the population receiving HZ vaccine and pneumococcal vaccine concomitantly.[22] Although the data are limited, coadministration of the tetanus and HZ vaccines has not resulted in either poor immune response

*Product monographs are reviewed and approved by Health Canada and contain information that might not be published or available in peer-reviewed journals.

or meaningful side effects; therefore, both can be administered at the same visit.[11]

7. What constitutes* immunocompromised *for vaccine contraindication? The ACIP states that people with primary or acquired immunodeficiency should not receive the vaccine. Those anticipating initiation of immunosuppressive therapy, or who have diseases that might lead to immunodeficiency, should receive 1 dose of HZ vaccine at least 14 days before beginning immunosuppressive therapy.[11] More detail is available in **Table 1.**[11,23] A heat-inactivated VZV vaccine is being investigated for use in immunocompromised populations.[16]

There remains a large "gray area" for mildly to moderately immunocompromised patients in whom the risk-benefit ratio of vaccination is not well understood. The potential risks of vaccinating patients receiving immunosuppressive drug therapies (eg, methotrexate or tumour necrosis factor–α inhibitors) or with illnesses that alter the immune system (eg, systemic lupus erythematosus or low-grade chronic lymphocytic leukemia) remain unknown. However, extreme old age (80 years of age and older) and the presence of medical comorbidities, such as diabetes mellitus, coronary artery disease, or hypertension, are not contraindications to vaccination.[16]

8. Can an adult receive the vaccine if there is an immunocompromised VZV-seronegative individual residing in the same household? Yes. Person-to-person transmission of the vaccine virus was not reported in HZ vaccine clinical trials. Postmarketing experience with varicella vaccine suggests that transmission (although rare) might occur between susceptible contacts and vaccinated individuals who develop a varicella-like rash.[10,11] After HZ vaccination, precautions are needed only if a varicella-like rash develops in individuals who are in close contact with people at risk of severe varicella.[11]

9. Can the vaccine cause the disease? The likelihood of vaccination causing a case of HZ appears to be very low. In clinical trials with Zostavax the vaccine strain of the virus was not detected in any of the postvaccination HZ-like rashes that were available for polymerase chain reaction testing.[10]

10. Can the vaccine be administered to patients taking antiviral medication? Antivirals active against HZ (acyclovir, famciclovir, and valacyclovir) might interfere with replication of the live VZV-based vaccine. Consequently, patients taking antiviral medications active against HZ should discontinue these medications for at least

Table 1. Possible contraindications for herpes zoster vaccination in immunocompromised patients

REASON FOR IMMUNODEFICIENCY	CAN THE VACCINE BE CONSIDERED IN THIS GROUP?
Bone marrow or lymphatic cancers (including leukemias and lymphomas)	No
Leukemia in remission and no radiotherapy or chemotherapy for at least 3 months	Yes
AIDS or manifestations of HIV (including CD4-positive T lymphocyte counts of less than 200/mm^3 or less than 15% of the total lymphocyte count)	No
Prednisone (or an equivalent corticosteroid): 20 mg/d or more for 2 or more weeks	No
Prednisone (or equivalent corticosteroid): less than 20 mg/d and not as chronic daily therapy*	Yes
Topical, intranasal, inhaled, and intra-articular corticosteroid use	Yes
Bursal or tendon corticosteroid injections	Yes
Methotrexate: more than 0.4 mg/kg weekly	No
Azathioprine: more than 3 mg/kg weekly	No
Mercaptopurine: more than 1.5 mg/kg weekly	No
Evidence (laboratory or clinical) of cellular immune deficiency	No
Impaired humoural immunity (eg, dysgammaglobulinemia, hypogammaglobulinemia)	Yes
Planned hematopoietic stem cell transplantation	Limited evidence—assess patient-relevant risk
2 or more years post–hematopoietic stem cell transplantation	Yes
Recombinant human immune mediators and immune modulators, particularly tumour necrosis factor inhibitors; the ACIP recommends deferring vaccination for at least 1 month after discontinuation of these therapies	No

ACIP—Advisory Committee on Immunization Practices, CD—cluster of differentiation.
*A clinical trial is under way to assess vaccination in individuals 60 years of age or older who are taking 5 to 20 mg of prednisone daily.[23]
Data from Harpaz et al.[11]

24 hours before the administration of the vaccine,[24] and should not restart them for at least 14 days after vaccination. Current NACI recommendations suggest that individuals taking antivirals at the time of vaccination might benefit from a second dose of vaccine at least 42 days after the first dose and after discontinuation of antiviral therapy.[1]

11. What happens if the vaccine is given intramuscularly instead of subcutaneously? Although the vaccine is meant to be administered subcutaneously, it is not necessary to repeat immunization if it is given intramuscularly.[10]

12. What about patients who take acetylsalicylic acid (ASA) on a daily basis—can they take this vaccine? Guidelines for the chickenpox (varicella) vaccine for children—which is different from the vaccine for adults—state that ASA should not be used to treat fever related to vaccinations in children because of the rare, but possible, association with Reye syndrome. This association does not exist with adults. Therefore, adults receiving long-term ASA therapy should be vaccinated if indicated.[25]

13. Should the HZ vaccine be given to people who have been immunized with a varicella virus vaccine? No. People who have immunity to chickenpox through vaccination do not appear to be at risk of severe HZ, and it is not recommended that they be vaccinated against shingles.[11] That said, health care providers do not need to inquire about previous VZV vaccination before administering the HZ vaccine, as so few people in the age group for which HZ vaccination is recommended have had VZV vaccination.[11]

14. Is the HZ vaccine stable outside the freezer? No. The vaccine must be maintained at a temperature of -15°C or colder, during shipping and storage. The diluents should be stored at room temperature (20°C to 25°C) or in the refrigerator (2°C to 8°C). Do not store the diluent in the freezer.[10]

Stability studies have shown that the HZ vaccine can be stored and transported at refrigerator temperature for up to 72 continuous hours before reconstitution. Vaccine stored in the refrigerator for more than 72 hours past removal from storage at -15°C should be discarded. Do not refreeze the vaccine.

The vaccine should be administered within 30 minutes after reconstitution in order to minimize loss of potency.

15. What side effects should physicians be concerned about? Overall, the HZ vaccine has a low incidence of side effects. The safety of the vaccine has been studied in more than 20 000 adults 50 years of age or older in clinical trials. In the SPS, injection site reactions (erythema, pain, swelling, pruritus, warmth, and hematoma) occurred in 48% of people who received the vaccine (versus 17% in the placebo arm).[10] Further details are provided in **Table 2.**[10,26]

16. How many people need to be vaccinated to prevent 1 case of HZ or PHN? To prevent 1 case of HZ and 1 case of PHN in individuals 65 years of age and older, 11 and 43 people, respectively, need to be vaccinated.[14]

17. Will the varicella immunization program affect the incidence of shingles? Some studies suggest that immunity to VZV is boosted through repeated exposure to varicella or HZ in adulthood. While it is plausible that a sufficient number of varicella exposures can reduce the risk of HZ in select populations, it remains unclear whether such levels of exposure have an

Table 2. Side effects observed with herpes zoster vaccination

SIDE EFFECT	TRIAL	INCIDENCE
Injection site reactions	SPS	48% in vaccinated group, 17% in placebo group; NNH = 3
• erythema		• 35.6%
• pain		• 34.3%
• swelling		• 26.1%
• pruritus		• 7.1%
• warmth		• 1.7%
• hematoma		• 1.6%
Headache	SPS	1.4% in vaccine group, 0.9% in placebo group; NNH = 167
Serious adverse events	SPS	1.4% in both vaccine and placebo groups; similar distribution
Hypersensitivity reactions (including anaphylactic reactions, fever, rash, and lymphadenopathy at the injection site)	Postmarketing surveillance	Uncommon to rare

NNH—number needed to harm, SPS—Shingles Prevention Study.
Data from the Zostavax product monograph.[10,26]

epidemiologically important role in reducing the risk of HZ among the general population of older adults.[11,27,28]

18. Should the vaccine be used in people older than the age of 80? Those older than 80 years are at the greatest risk for HZ and PHN. The effectiveness of the HZ vaccine in adults older than 80 years was unclear in the SPS trial; however, a recent large retrospective cohort study for Zostavax demonstrated that vaccine effectiveness was maintained across all age strata, including the oldest vaccine recipients ($P = .62$).[29]

Neither Health Canada nor NACI have set an upper age limit on the use of the vaccine,[1] while the ACIP recommends that the vaccine be offered to all eligible people, including older individuals, frail individuals, and individuals with chronic illnesses.[21] Heterogeneity of health makes age criteria much less helpful. A "nonfrail" 85-year-old might derive similar or enhanced benefit from the vaccine compared with a "frail" 75-year-old.

Conclusion

The HZ vaccine is safe and effective in reducing the incidence of HZ and PHN, as well as in attenuating the severity of HZ disease in older adults. The NACI advises that the vaccine be recommended for all adults aged 60 years and older and be considered in those older than 50 years.[1]

In Canada, direct medical costs are approximately $68 million annually for the diagnosis and treatment of HZ and its complications.[2] As a prevention strategy, the HZ vaccine is both complicated (owing to cold-chain requirements) and costly (approximately $150 per person), as the vaccine is not publicly funded. However, results of economic studies suggest that vaccinating adults with the HZ vaccine, especially individuals aged 60 to 75 years, is a cost-effective intervention and a judicious use of scarce health care resources, particularly in light of the large aging population.[30,31]

The data support HZ vaccination as a feasible and safe prevention strategy for reducing the overall burden of HZ. Herpes zoster vaccination should become an integral part of the promotion of healthy aging.

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