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Vaccination against herpes zoster in developed countries

State of the evidence

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Although progress has been made in the treatment of herpes zoster (HZ) and postherpetic neuralgia (PHN), available therapeutic options are only partially effective. Given evidence that a live-attenuated varicella-zoster-virus vaccine is effective at reducing the incidence of HZ, PHN and the burden of illness, policymakers and clinicians are being asked to make recommendations regarding the use of the zoster vaccine. In this report, we summarize the evidence regarding the: (1) burden of illness; (2) vaccine efficacy and safety; and (3) cost-effectiveness of vaccination, to assist evidence-based policy making and guide clinicians in their recommendations. First, there is general agreement that the overall burden of illness associated with HZ and PHN is substantial. Second, the safety and efficacy of the zoster vaccine at reducing the burden of illness due to HZ and the incidence of PHN have been clearly demonstrated in large placebo-controlled trials. However, uncertainty remains about the vaccine's duration of protection. Third, vaccination against HZ is likely to be cost-effective when the vaccine is given at approximately 65 y of age, if vaccine duration is longer than 10 y.

since the time of primary infection.^{1,2} It is characterized by dermatomal pain and vesicular rash.^{3,4} The most common complication of HZ is postherpetic neuralgia (PHN),^{5,6} often defined as clinically significant pain persisting more than 90 d after rash onset.⁷ HZ can also lead to other complications, particularly in immunosuppressed individuals. These include disseminated zoster, ophthalmic zoster, motor paresis (including facial paralysis) and inflammation of the spinal cord and brain.⁸

Although progress has been made in the treatment of HZ and PHN, available therapeutic options are only partially effective. Aggressive treatment with antivirals (famciclovir, valacyclovir) reduces acute pain and hastens rash resolution, but their ability to prevent the development of PHN remains controversial.⁹ In addition, antiviral therapy is most effective when initiated within 72 h of HZ rash onset, but the diagnosis of HZ is often delayed.¹⁰ PHN is debilitating and its management is often unsuccessful, despite the combined use of tricyclic antidepressants, gabapentinoids, strong analgesics such as opioids and topical agents such as lidocaine medicated plasters or high-concentration capsaicin patches.^{8,11-13}

Given evidence that a live-attenuated VZV vaccine (zoster vaccine) is effective at reducing the incidence of HZ, PHN and

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Herpes zoster (HZ), or shingles, results from reactivation of the varicella-zoster virus (VZV) latent in sensory ganglia

Table 1. Evolution of pain over the course of the disease^{19,33,36}

	Phases of the disease			
	Prodromal	Acute	Sub-acute	Postherpetic
Days since rash onset	Prior to rash	0–30 d	31–90 d	> 90 d
Had pain at the beginning of the phase (%)	74%	95%	58%	24%
Mean pain severity (/10)*	5.9	6.3	3.8	3.8
Median pain duration (days)	5 d	33 d		77 d [†]

*Mean pain severity (ZBPI worst pain score) estimated among individuals reporting clinically significant pain (i.e., worst ZBPI score ≥ 3) during each phase of the disease. [†]77 d is the median duration of pain after the first 90 d of acute and subacute pain.

the burden of illness due to HZ,¹⁴ vaccination against HZ is promising. In many countries, policymakers and clinicians are being asked to make recommendations regarding the use of the zoster vaccine, in the light of competing demands on limited public health resources. The main criteria considered in recommendations of immunization programs include the: (1) burden of illness; (2) vaccine efficacy and safety; and (3) cost-effectiveness of vaccination. In this report, we summarize the information available for each of the above criteria to assist evidence-based policymaking and guide clinicians in their recommendations in developed countries.

Burden of Illness

Epidemiology of herpes zoster and postherpetic neuralgia. The age-specific incidence of HZ is highly consistent between developed countries.^{8,15,16} About 20–35% of individuals living in developed countries will develop HZ at some point in their life^{8,15,16} and complications of HZ occur in 13–40% of cases.^{6,17,18} PHN is the most common complication, with 8 to 27% of individuals with HZ developing PHN.^{14,19–21} Moreover, the risk of developing PHN as a complication of HZ increases markedly with age; it is about four times higher among individuals older than 70 y of age compared with those younger than 60.^{15,21}

The overall incidence of HZ has been increasing for a number of years.^{16,22,23} For example, the incidence of HZ consultations in the US increased from 1.7 in 1993 to 4.4 per 1000 person-year in 2006, and is rising in most age groups.²² Although the cause of the rise in HZ remains unclear, it has been suggested that it may

be due to: (1) the aging of the population, (2) increasing numbers of immunocompromised individuals in the population and, (3) decreasing exposure to childhood varicella. First, since the incidence rate of HZ increases with age, increasing age of the population in most developed countries will likely lead to a greater number of cases. Second, changes in the management of malignant or auto-immune diseases, as well as the increasing use of corticosteroids and immunosuppressant medication (particularly for organ transplants) are all likely to increase the number of immunocompromised subjects, at greater risk of HZ.^{23,24} Finally, although still controversial, several epidemiological studies support the hypothesis that exposure to childhood varicella reduces the risk of developing HZ by boosting immunity against VZV.^{25,26} Exposure to childhood varicella has been decreasing due to important demographic and societal changes in industrialized countries (e.g., decreasing proportions of women with at least one child, decreasing numbers of children per woman, increasing numbers of single-parent families and decreasing contact between grandparents and grandchildren) and the introduction of routine childhood varicella vaccination. However, a clear association between childhood varicella vaccination and the increase in age-specific incidence of HZ has yet to be established.^{22,27–29} Close monitoring of HZ in countries that have introduced childhood varicella vaccination will help improve our understanding of the impact of these different factors on HZ incidence.

Burden of illness from the patient perspective. Prodromal pain. Prodromal pain, which reflects the reactivation of latent VZV and its subsequent replication in

neural tissue, is reported by most patients with HZ.^{24,30–32} In MASTER (Monitoring and Assessing Shingles Through Education and Research), a pan-Canadian prospective observational study, 74% of individuals experienced prodromal pain, most often described as a burning, itching or shooting sensation³³ (Table 1). This pain generally begins 4–6 d before rash onset, with a mean severity of approximately 6 out of 10.³³ Older individuals, the unemployed and/or those with impaired immune status were more likely to report prodromal pain³³ (Table 2). Because the identification of prodromal pain as a manifestation of HZ is only possible when the HZ rash appears, prodromal HZ is often misdiagnosed and mistaken for other diseases associated with unilateral pain, such as angina, renal stones, cholecystitis, or lumbar radiculopathy.³⁴ However, it is frequent and contributes to the overall burden of illness of HZ.³³ Finally, prodromal pain and greater severity of this pain are generally recognized as markers of more severe HZ and PHN.^{33–35}

Acute and subacute phases of HZ. Acute phase of HZ is characterized by a unilateral, dermatomal and vesicular rash, most often accompanied by pain or discomfort.³⁴ Acute HZ pain probably results from a combination of nociceptive pain due to the inflammation of the skin and neuropathic pain caused by neuronal damage.³⁰ The pain can be intermittent or constant and is often described as a burning, itching, shooting or throbbing sensation. Allodynia, which is defined as pain in response to a normally non-painful stimulus, is also commonly reported in the area of the HZ rash.³⁴ Virtually all subjects in MASTER reported pain at recruitment, with 45%, 39% and 11% reporting, severe, moderate and mild pain.³⁶

The rash and pain associated with HZ generally disappear within one month, although pain may persist for several weeks, months, or even years after the rash has healed in some patients.^{34,36} In MASTER, the severity of pain decreased significantly during the first 30 d after rash onset, from an average of 6.3/10.0 to 2.4/10.0. Between 30 and 90 d, the mean pain severity continued to decrease significantly, but at a slower rate. Median duration of pain was 33 d (Table 1), which is

consistent with other studies using similar methods.^{37,38} Individuals of lower socioeconomic status, who were immunocompromised, and those with a greater number of lesions were more likely to report severe acute pain (Table 2). Interestingly, age was not associated with the severity of acute pain, with younger patients as likely as older ones to experience a considerable burden of illness during the acute phase of HZ.^{36,39}

Acute HZ has a major impact on quality of life and functional status.⁴⁰⁻⁴³ For example, among individuals who did not develop PHN in MASTER, 95%, 51% and 44% reported, at recruitment (i.e., within 14 d of rash onset), pain and discomfort, problems in performing their usual activities and symptoms of anxiety and depression, respectively, compared with 32%, 10% and 22% prior to HZ⁴² (Fig. 1). These proportions returned to pre-HZ values after pain cessation. Significant impairments across different age groups also indicated that younger patients were as likely as older ones to be adversely affected during the acute phase of HZ.⁴² In accordance with data from Schmader et al.,⁴⁰ the majority of participants in MASTER reported interference with sleep (64%), enjoyment of life (58%) and general activities (53%)⁴² during the acute phase of HZ. A few studies also indicated that HZ had a negative impact on productive work life.⁴⁴⁻⁴⁷ In these studies, the great majority of employed individuals with HZ reported missing time off work for a mean absenteeism of 26 to 32 h per employee.⁴⁴⁻⁴⁷ Moreover, presenteeism (i.e., time with decreased effectiveness at work because of illness^{48,49}) has been reported to affect 72% of employed individuals during the acute phase of HZ, with a mean of 22 h of presenteeism per employee.⁴⁷

Postherpetic neuralgia. PHN is the most common debilitating complication of HZ, one of the most challenging to treat and the cause of the greatest HZ-related burden of illness. However, controversy exists regarding the exact definition of PHN. Furthermore, the instruments used to measure PHN greatly differ between studies and the overall risk varies according to the age distribution of the studied group. For these reasons, important variations

Table 2. Predictors of higher burden of illness for the different phases of herpes zoster^{19,33,36}

Potential predictors	Outcomes			
	Prodromal pain	Acute pain	Subacute pain	PHN
Socio-demographic characteristics				
Older age	↑	—	↑↑	↑↑
Women	—	—	—	—
Lower income/education	↑	↑↑	↑↑	↑
Being unemployed	↑↑	—	—	—
General health prior to HZ				
Impaired immune status	↑↑	↑↑	↑↑	↑↑
Other pain condition	—	—	—	—
Limitations in functional activities	—	—	—	↑↑
Characteristics of HZ				
Reported prodromal pain	NA	↑	↑	↑
Greater number of lesions	NA	↑↑	↑	—
Severity of pain at recruitment	NA	↑↑	↑↑	↑↑
Dermatome affected	NA	—	—	—
Initial treatment of HZ				
Antivirals	NA	—	↓	↓
Others	NA	—	—	—

NA, non-applicable. One arrow indicates significant association with the outcome in univariate analysis and two arrows indicate significant association with the outcome in univariate and multivariate analysis.

in the estimated risk of developing PHN (from 8 to 27%^{14,19,20,32}) are found in the literature. This has led to conflicting messages to health professionals and difficulty in quantifying the burden of PHN. In MASTER, the risk of developing PHN was 22% among immunocompetent participants, when defined as a worst pain score $\geq 3/10$ during the last 24 h (as measured by the Zoster Brief Pain Inventory (ZBPI)⁷) persisting more than 90 d after rash onset.¹⁹ However, this risk decreased to 14% when defined by the average pain during the last 24 h or by current pain (also measured by the ZBPI). These observations illustrate that methodological choices can largely influence the estimates of the risk of PHN, and therefore should be taken into account when comparing studies.

Very few clinical studies have estimated the complete duration and burden of PHN, due to the prohibitive cost of following-up PHN patients for years.^{18,50}

Helgason et al. estimated that the average duration of PHN is about 1.5 y.⁵⁰ At the beginning of the PHN period, 69% of subjects in MASTER reported moderate pain and 15% reported severe pain. In addition, half of subjects with PHN still reported clinically significant pain at the end of study follow-up (i.e., 180 d after rash onset).¹⁹ Older age, greater rash severity and greater acute pain have been consistently identified as predictors of PHN.^{19,32,50-54} Other risk factors, such as prodromal pain,³² female gender³² and ophthalmic localization of HZ rash³² were identified only in some studies. In addition, MASTER results indicated that reduced premorbid functional status, possibly a marker of poor health or immune function, also increased the risk of developing PHN.¹⁹

Clinical observations suggest that PHN has a severe impact on several aspects of quality of life and on functional status.⁵⁵ For example, individuals with PHN often

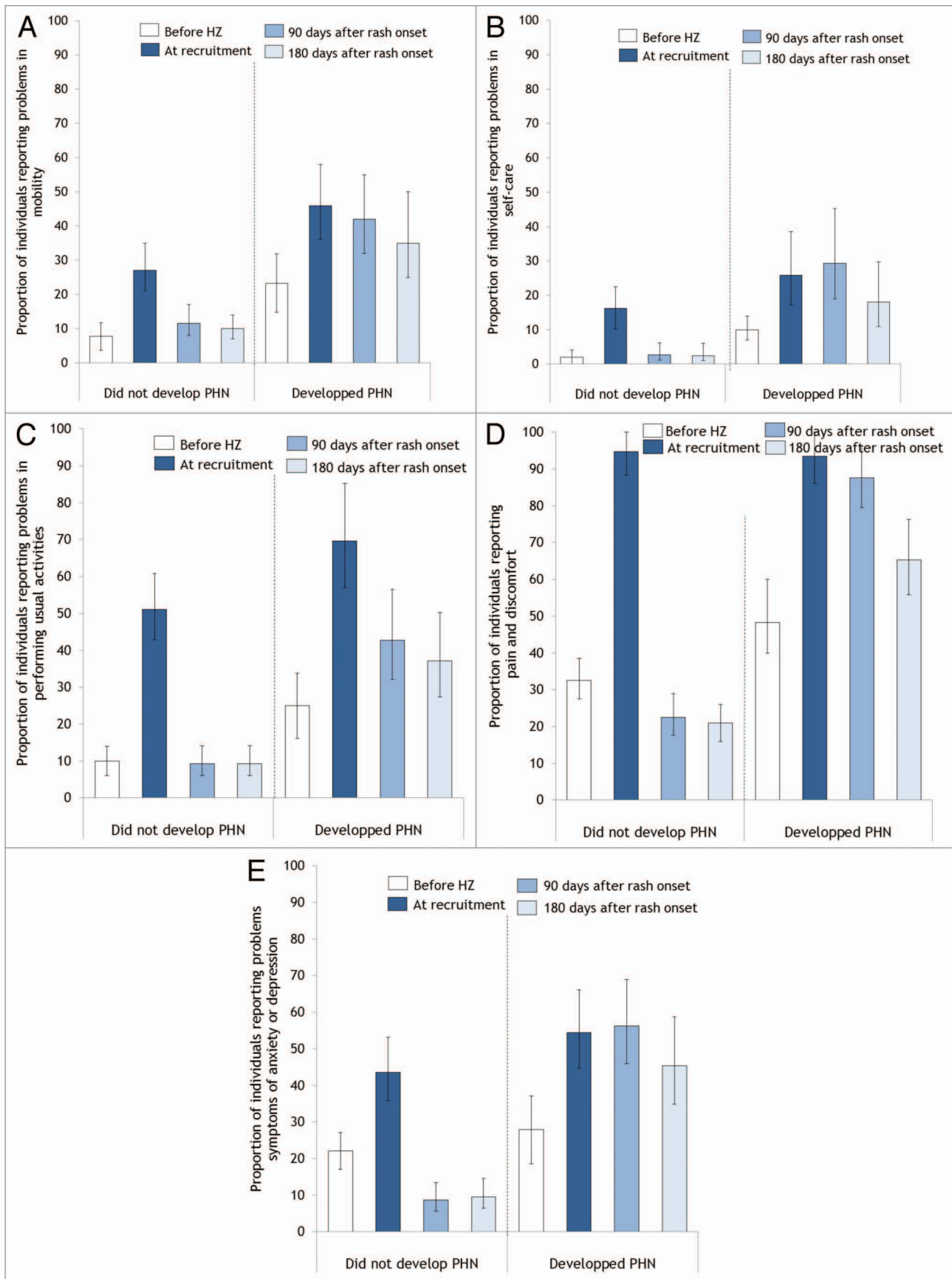


Figure 1. Impact of herpes zoster and postherpetic neuralgia on the quality of life. (A) Problems in mobility (B) Problems with self-care (C) Problems in performing usual activities (D) Pain and discomfort (E) Anxiety and depression.

Table 3. Herpes zoster vaccine efficacy according to age at vaccination^{14,62}

Age	Incidence of HZ			Burden of illness*			Incidence of PHN		
	Vaccine	Placebo	VE (95% CI)	Vaccine	Placebo	VE (95% CI)	Vaccine	Placebo	VE (95% CI)
50–59 y	1.99	6.60	70 (54–81)	0.13	0.49	73 (53–85)	NA	NA	NA
60–69 y	3.90	10.79	64 (56–71)	1.50	4.33	66 (52–76)	0.26	0.74	66 (20–87)
≥ 70 y	7.18	11.50	38 (28–52)	3.47	7.78	55 (40–67)	0.71	2.13	67 (43–81)

*Burden of illness score is a composite measure of the incidence of HZ, severity and duration of pain. NA, The efficacy of the vaccine at preventing PHN was not assessed among younger subjects given the prohibitively large sample size needed to detect an effect.

report a variety of symptoms such as sleeping problems, chronic fatigue, anorexia, weight loss, anxiety and depression.⁵⁵ Furthermore, the social life of individuals with PHN is often seriously affected by the disease.⁵⁵ However, very few studies have quantified the magnitude of these clinical observations.^{42,43,56} In MASTER, all five health domains assessed by the Euroqol^{57,58} were significantly affected during PHN.⁴² For example, at the onset of PHN (i.e., 90 d after rash onset), significantly higher proportions of individuals reported anxiety and depression (56%) and problems with self-care (29%), compared with 28% and 10% prior to HZ (Fig. 1). Interestingly, individuals who developed PHN were more likely to report problems in different health domains prior to HZ compared with those who did not develop PHN (Fig. 1). These data once again support the hypothesis that limitations in pre-morbid functional status may increase the risk of developing PHN. Consistent with data from Bouhassira et al. and Johnson et al., PHN also interfered with enjoyment of life (31%), mood (30%), sleep (29%) and general activity (25%).^{42,43,56} Finally, PHN has a negative impact on the productive life of individuals.⁴⁷ In MASTER, employed subjects who developed PHN reported absenteeism and presenteeism for a mean of 36 and 122 h per employee.⁴⁷

Impact of herpes zoster and postherpetic neuralgia on the healthcare system. In addition to the burden of HZ and PHN from the patient's perspective, the management of these conditions results in important costs for the health care system. The main cost drivers of HZ and its complications include outpatient physician visits, hospitalizations and drug prescriptions. In the US, the healthcare cost per acute episode was estimated to be \$431 (\$US 2007).⁷⁵ In UK, the average costs

for treating HZ and PHN were estimated at £75 and £340 per case (£ 2009).⁵⁹ In Canada, the diagnosis and treatment of HZ and its complications was estimated to cost \$521 per episode for an annual cost of \$68 million (\$CAN 2009).⁶⁰ Most of health care use is among adults over the age of 60 y.^{15,60,61} In Canada, about 40% of HZ consultations, 75% of HZ hospitalization and 71% of PHN episodes occur in adults over 60 y of age.⁶⁰

Herpes Zoster Vaccine Efficacy and Safety

The Shingles Prevention Study (SPS), a randomized, double-blind, placebo-controlled trial, conducted among 38,546 adults ≥ 60 y of age, showed that a live-attenuated zoster vaccine was effective at reducing the incidence of HZ and PHN by 51% and 66%, respectively.¹⁴ In addition, the vaccine significantly reduced the burden of illness, a composite measure of incidence, duration and intensity of pain by 61%¹⁴ (Table 3). A second randomized, placebo-controlled trial, conducted among 22,439 individuals aged 50–59 y old also showed that the zoster vaccine was effective at reducing the incidence of HZ and the burden of illness by 70% and 73%, respectively among these younger subjects.⁶² As illustrated in Table 3, the vaccine efficacy at preventing HZ significantly decreased with older age at vaccination, but was similar for the burden of illness and prevention of PHN across the different age groups.⁶³ These results suggest that, for younger individuals, most of the benefit of HZ vaccination resulted from the reduction of HZ incidence, whereas for older individuals, much of the benefit resulted from the reduction in disease severity and the incidence of PHN incidence. Furthermore, the zoster

vaccine significantly reduced the burden of HZ-related interference with activities of daily living in the overall population of vaccinees, as well as in individuals who developed HZ.⁶⁴ The Short-Term Persistence Substudy (STPS), a continuation of follow-up of 14,000 SPS subjects, confirmed that vaccine efficacy was maintained through year 5 after vaccination. However, a decline in vaccine efficacy was observed over the 5-y follow-up, particularly for vaccine efficacy against HZ. Because of the small number of cases observed during the STPS, the study power was insufficient to draw conclusion about the persistence of vaccine efficacy beyond 5 y post-vaccination.⁶⁵ These results seem to confirm a modeling study, which estimated that the zoster vaccine protection waned over time.⁶⁶

The vaccine was well tolerated in the SPS with similar proportions of participants who received the zoster vaccine (n = 19,270) or the placebo (n = 19,276) reporting serious adverse events (1.4% for both, zoster vaccine and placebo groups).¹⁴ Varicella-like rash at the site of injection was the only adverse event statistically more frequent in the vaccinated arm (0.1%) compared with the placebo group (0.04%). The safety of the vaccine was confirmed in the clinical trial among younger subjects with similar proportions of serious adverse events occurring after vaccination (zoster vaccine: 0.6%; placebo: 0.5%).⁶²

Cost-Effectiveness of Vaccination against Herpes Zoster

Many studies have examined the cost-effectiveness of vaccination against HZ.^{15,59–61,67–74} These studies report that the incidence, morbidity and costs associated with the management of HZ and PHN

are substantial. Furthermore, they suggest that HZ vaccination is cost-effective if given at 60–70 y of age, assuming vaccine duration of protection is longer than 10 y and vaccine efficacy against PHN is around 67% across all ages.^{15,59,60,67,69}

For a given country, the cost-effectiveness of HZ vaccination is highly sensitive to three key elements: age at vaccination, vaccine duration of protection and vaccine efficacy against PHN. Given that the incidence of HZ and risk of PHN increase markedly after 60 y of age, the optimal age at vaccination is the one that strikes the optimal balance between higher vaccine efficacy among younger individuals and possible waning of vaccine protection. Thus, most studies suggest that the optimal age at HZ vaccination is at around 65 y.^{15,59,60} Vaccination beyond 65 y of age is less cost-effective as a result of decreasing vaccine efficacy and shorter life expectancy. On the other hand, vaccination before the age of 65 y is less cost-effective because of the uncertainties related to duration of vaccine protection. Duration of the vaccine efficacy, particularly against PHN, has a great impact on cost-effectiveness estimates and contributes most to the uncertainty regarding the cost-effectiveness of HZ vaccination. The recent results from the STPS, indicating possible waning of protection against HZ over time,⁶⁵ can thus have an important impact on whether the vaccine is cost-effective. However, the key to zoster vaccine cost-effectiveness is the efficacy against PHN across older age groups and the duration of this efficacy.

Conclusion

In light of the current evidence, vaccination against HZ is promising. First, there is general agreement that the overall burden of illness associated with HZ is substantial, not only for individuals who will develop PHN, but also during the prodromal and acute phases of HZ. Available therapeutic options are only partially effective, and the management of PHN is complex and often unsuccessful. Severe detriments to the quality of life have been reported throughout the course of HZ, and the economic burden is substantial. Second, the safety profile of the vaccine

and its efficacy at reducing the burden of illness due to HZ and the incidence of PHN have been clearly demonstrated in large placebo-controlled trials. However, uncertainty remains about the vaccine's duration of protection against HZ and, more importantly, PHN. More research is needed to estimate the duration of protection against PHN, through long-term follow-up and through modeling studies of decay of vaccine protection. Third, vaccination against HZ is likely to be cost-effective when the vaccine is given at approximately 65 y of age, assuming average vaccine protection against moderate/severe pain and PHN is longer than 10 y.

Disclosure of Potential Conflicts of Interest

Drs Drolet and Patrick have no conflicts of interest to declare. Dr Oxman has consulted for Merck Frosst and is national chairman of the Shingles Prevention Study (VA Cooperative Study no. 403) and its substudies, which have been supported in part by grants from Merck to the VA Cooperative Studies Program, to the VA San Diego Medical Research Foundation and to the VA Connecticut Research and Education Foundation. Dr Levin has consulted for Merck Frosst; he has received research funds from Merck and is on their speakers bureau. Dr Schmader has received grant support from Merck and Wyeth and has consulted for Merck and GlaxoSmithKline. Dr Johnson has consulted and has received honoraria for public speaking from Merck Frosst, Merck (US), Sanofi Pasteur Merck, Astellas, Novartis and GlaxoSmithKline. Dr Mansi was an employee of Merck Frosst Canada Ltd. Dr Brisson has consulted and received reimbursement for travel expenses from Merck Frosst and GlaxoSmithKline.

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steering committee was responsible for the development of the study protocol and for the direction of MASTER. Merck Frosst Canada Ltd. does not have any ownership rights to the findings and results of MASTER. The scientific steering committee has absolute discretion and the final decision over the contents and authorship of all publications or presentations.

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