Herpes Zoster Vaccination: A Vaccine to Prevent Pain

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Is it desirable to prevent or attenuate herpes zoster, and if yes, is it possible by vaccination?

The varicella zoster virus (VZV) is an alpha herpesvirus that forms latency and can reactivate to cause a second infection. The alpha part of the name is important, as it places this virus in the same category as herpes simplex virus (HSV): both are neurotropic. The primary infection with VZV is varicella (chicken pox) and is usually, but not always, associated with full recovery. Reactivation occurs in the form of herpes zoster (HZ), commonly known as "shingles". In younger patients, shingles is often a painful rash that lasts 10–20 days and is usually followed by full recovery, albeit with the possibility of some hypo- or hyperpigmentation. However, in older and immunocompromised patients, post-herpetic neuralgia (PHN) is a common complication. Latency of the virus following primary infection occurs in sensory ganglia, but reactivation and neural transmission result in changes of neural architecture and function in the skin, the primary afferent nerve, and the sensory ganglion, where a large volume of normal neural tissue is replaced by scar tissue. In the spinal cord, the dorsal horn of the ipsilateral side can show atrophy.

VZV seropositivity, a marker of the presence of latent virus, is a prerequisite for the development of shingles. Most people become seropositive by the time they are adults, with more than 90% of children in temperate regions contracting chickenpox in the first 10–12 years of life [1]. Thus, the vast majority of people have the potential to develop shingles, and approximately one third of seropositive subjects do during their lifetime. The incidence of HZ increases with age, particularly beyond 60 and 70 years of age, with rates of approximately 3.2/1000 person-years overall and up to 10/1000 person-years above 80 years [2, 3]. The age-adjusted incidence of zoster has been shown to be increasing [4, 5].

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J.-P. Michel, S. Maggi (eds.), *Adult Vaccinations*, Practical Issues in Geriatrics,
https://doi.org/10.1007/978-3-030-05159-4_15

Humans experience a natural decline in immunity with ageing, known as immunosenescence. This phenomenon affects both non-pathogen-specific innate immunity and pathogen-specific adaptive immunity [6]. Immunosenescence can affect both the number and function of immune cells, resulting in increased morbidity and mortality from infection and reduced vaccine responsiveness [7–9].

About 10% of shingles cases are not related to ageing but rather to immunosuppressive disease or immunosuppressant treatment. In an age-, sex-, calendar time-, and practice-matched case–control study from UK primary care, Hansson et al. estimated the association between 21 of the most common specific malignancies and subsequent zoster risk [10]. They found that malignancy overall was associated with an increased risk of zoster (adjusted odds ratio (OR) 1.29, 95% confidence interval (CI) 1.27–1.32), with haematological malignancies associated with an especially high risk [10]. However, the magnitude of the associations varied widely, and the strength of the association decreased as patient age increased.

Recurrent cases of HZ have been reported, with various studies suggesting recurrence rates ranging from 1 to 6% in immunocompetent individuals [11–13]. Recurrence is reported to be more frequent in women [12].

A frequent complication of HZ is post-herpetic neuralgia (PHN). It is difficult to ascertain the true rates of PHN incidence, since comparisons across studies are precluded by the lack of a standardized definition of PHN. Rates of PHN vary widely between studies [2, 3, 14–19], but it is clear that the older the patient, the longer the pain lasts after the zoster episode [20]. The current accepted definition of PHN is clinically significant pain (worst pain score ≥3 on a 0–10 scale where 10 represents worst imaginable pain) occurring or persisting at or beyond 90 days after HZ rash appearance. The main predictors for PHN are greater disease severity (pain and rash) and older age, while other factors such as female sex or immunosuppression have also been found to be associated with an increased risk [20, 21]. Prevalence of PHN for individuals aged ≥50 years is approximately 24% at 90 days after rash appearance and 11% at 180 days [22].

Other complications, although much less common, may nonetheless be serious and include neurological complications (other than PHN), such as an increased risk of stroke in the 6–12 months after HZ infections, encephalitis, cranial and motor neuron palsies or hearing loss. Ophthalmic complications, such as keratitis, uveitis or retinal necrosis leading to significant sight loss may sometimes accompany ophthalmic zoster. Cutaneous complications are seen, including bacterial superinfection or scarring. Visceral complications, which are very rare, may include myocarditis, pericarditis, arthritis or hepatitis.

The impact of HZ and PHN is far-reaching, affecting not only the patient but also the patient's family and caregivers, the healthcare economy and even employers via absenteeism or loss of productivity (presenteeism). Since retirement age is continually rising, more and more people with shingles will be among the working population, resulting in further loss of productivity. Functional ability declines with age, and HZ and PHN may accelerate this decline, and many patients will never regain the level of functioning appropriate for their age.

The MASTER study performed in Canada was a multicentre prospective cohort study of 261 HZ patients aged 50 years or over from 83 physician offices. The Zoster Brief Pain Inventory was used to measure severity of pain and interference with activities of daily living (ADL) because of pain, and the EuroQol EQ-5D assessment tool was used to measure quality of life [23]. The questionnaires were administered at regular intervals up to 180 days post-recruitment. Those patients who developed PHN, compared with those who did not, had significantly greater reduction in ADL from onset of HZ [23]. Overall, age-adjusted absenteeism- and presenteeism-related work loss was estimated at 31.6 h and 84.4 h, respectively, with a combined work loss of 116.0 h per HZ episode in a working person of 50–64 years of age [24]. This corresponds to about 3 weeks of lost work productivity for shingles, and it is also expensive in terms of healthcare expenditure. Indeed, in a study by Gialloreti et al., the direct costs of HZ (without PHN) were estimated at 122.68 ± 97.51 € for outpatient cases and more than 20 times higher (mean 2592 ± 1313 €) for patients requiring inpatient care [15]. Patients experiencing PHN incurred even higher costs, with an extra cost of 446 ± 442 € per episode of PHN in outpatients and 2806 ± 2641 € per PHN episode in inpatients. These data confirm the considerable financial burden resulting from HZ and PHN.

For the management of PHN, there exist a number of oral and topical therapies that have been shown to be superior to placebo for the treatment of PHN and neuropathic pain in general, but they have modest efficacy and often have a narrow therapeutic index. Indeed, most patients do not achieve adequate pain relief. In addition, in older patients with concomitant medication, adverse events are common. However, there is increasing evidence that sensory profiling using quantitative sensory testing (QST) may be able to predict response to treatment at the individual level in patients with neuropathic pain [25]. There is a lack of evidence supporting psychological or invasive therapies, including neuromodulation, in neuropathic pain.

There is clearly a rationale for vaccination against HZ. Available vaccines are the live attenuated VZV vaccine (Zostavax®) and the recently approved subunit adjuvanted vaccine (Shingrix®). Zostavax has been demonstrated to reduce incidence of HZ in immunocompetent adults ≥60 years by HZ by 51.3% ($P < 0.001$) and PHN by 66.5% ($P < 0.001$). It is more effective in younger than older subjects. At age 60–69 years, efficacy for HZ is 63.9 (90% CI 56–71) and above 70 years, 37.6 (90% CI 28–52). For PHN, efficacy is similar at all ages. Reactions at the injection site were more frequent among vaccine than placebo recipients but were generally mild [26]. Effectiveness studies have produced similar results.

Shingrix® is very effective, with overall vaccine efficacy against HZ of 97.2% (95% CI 93.7–99.0; $P < 0.001$), at age 60–69 years 97.4% (90.1–99.7, $P < 0.001$) and above 70 years 97.9% (87.9–100.0, $P < 0.001$) [27]. Without HZ one cannot develop PHN. Shingrix is significantly more reactogenic than Zostavax under study conditions. Nonetheless, 91% of patients with severe reaction returned for the second injection. Two doses of vaccine 2 months apart are required. There was no increased reactogenicity after the second injection. There was no evidence of increased immune-mediated diseases or exacerbation thereof [27]. Effectiveness

studies are not available as the vaccine has only recently been licensed. It is likely that Shingrix will be suitable for protection of immunocompromised subjects.

Overall, with our current state of knowledge, we can confidently say that HZ is worth preventing. In answer to the question as to whether it is possible to prevent it through vaccination, the answer is yes for those whom the vaccine is available. Some at-risk populations may not have this advantage, thus underlining the compelling need to pursue research on possible drugs effective in managing HZ and its complications.

References

1. Sengupta N, Booy R, Schmitt HJ, Peltola H, Van-Damme P, Schumacher RF, et al. Varicella vaccination in Europe: are we ready for a universal childhood programme? Eur J Pediatr. 2008;167(1):47–55.
2. Gauthier A, Breuer J, Carrington D, Martin M, Remy V. Epidemiology and cost of herpes zoster and post-herpetic neuralgia in the United Kingdom. Epidemiol Infect. 2009;137(1):38–47.
3. Stein AN, Britt H, Harrison C, Conway EL, Cunningham A, Macintyre CR. Herpes zoster burden of illness and health care resource utilisation in the Australian population aged 50 years and older. Vaccine. 2009;27(4):520–9.
4. Yawn BP, Saddier P, Wollan PC, St Sauver JL, Kurland MJ, Sy LS. A population-based study of the incidence and complication rates of herpes zoster before zoster vaccine introduction. Mayo Clin Proc. 2007;82(11):1341–9.
5. Lu PJ, Euler GL, Harpaz R. Herpes zoster vaccination among adults aged 60 years and older, in the U.S., 2008. Am J Prev Med. 2011;40(2):e1–6.
6. Aspinall R, Del Giudice G, Effros RB, Grubeck-Loebenstein B, Sambhara S. Challenges for vaccination in the elderly. Immun Ageing. 2007;4:9.
7. Caruso C, Buffa S, Candore G, Colonna-Romano G, Dunn-Walters D, Kipling D, et al. Mechanisms of immunosenescence. Immun Ageing. 2009;6:10.
8. Kumar R, Burns EA. Age-related decline in immunity: implications for vaccine responsiveness. Expert Rev Vaccines. 2008;7(4):467–79.
9. Boraschi D, Del Giudice G, Dutel C, Ivanoff B, Rappuoli R, Grubeck-Loebenstein B. Ageing and immunity: addressing immune senescence to ensure healthy ageing. Vaccine. 2010;28(21):3627–31.
10. Hansson E, Forbes HJ, Langan SM, Smeeth L, Bhaskaran K. Herpes zoster risk after 21 specific cancers: population-based case-control study. Br J Cancer. 2017;116(12):1643–51.
11. Kawai K, Gebremeskel BG, Acosta CJ. Systematic review of incidence and complications of herpes zoster: towards a global perspective. BMJ Open. 2014;4(6):e004833.
12. Shiraki K, Toyama N, Daikoku T, Yajima M, Miyazaki Dermatologist S. Herpes zoster and recurrent herpes zoster. Open Forum Infect Dis. 2017;4(1):ofx007.
13. Yawn BP, Wollan PC, Kurland MJ, St Sauver JL, Saddier P. Herpes zoster recurrences more frequent than previously reported. Mayo Clin Proc. 2011;86(2):88–93.
14. Helgason S, Petursson G, Gudmundsson S, Sigurdsson JA. Prevalence of postherpetic neuralgia after a first episode of herpes zoster: prospective study with long term follow up. BMJ. 2000;321(7264):794–6.
15. Gialloreti LE, Merito M, Pezzotti P, Naldi L, Gatti A, Beillat M, et al. Epidemiology and economic burden of herpes zoster and post-herpetic neuralgia in Italy: a retrospective, population-based study. BMC Infect Dis. 2010;10:230.
16. Opstelten W, Mauritz JW, de Wit NJ, van Wijck AJ, Stalman WA, van Essen GA. Herpes zoster and postherpetic neuralgia: incidence and risk indicators using a general practice research database. Fam Pract. 2002;19(5):471–5.

17. Ultsch B, Koster I, Reinhold T, Siedler A, Krause G, Icks A, et al. Epidemiology and cost of herpes zoster and postherpetic neuralgia in Germany. Eur J Health Econ. 2013;14(6):1015–26.
18. Weitzman D, Shavit O, Stein M, Cohen R, Chodick G, Shalev V. A population based study of the epidemiology of Herpes Zoster and its complications. J Infect. 2013;67(5):463–9.
19. Yawn BP, Gilden D. The global epidemiology of herpes zoster. Neurology. 2013;81(10):928–30.
20. Meister W, Neiss A, Gross G, Doerr HW, Hobel W, Malin JP, et al. A prognostic score for postherpetic neuralgia in ambulatory patients. Infection. 1998;26(6):359–63.
21. Forbes HJ, Bhaskaran K, Thomas SL, Smeeth L, Clayton T, Mansfield K, et al. Quantification of risk factors for postherpetic neuralgia in herpes zoster patients: a cohort study. Neurology. 2016;87(1):94–102.
22. Drolet M, Brisson M, Schmader K, Levin M, Johnson R, Oxman M, et al. Predictors of postherpetic neuralgia among patients with herpes zoster: a prospective study. J Pain. 2010;11(11):1211–21.
23. Drolet M, Brisson M, Schmader KE, Levin MJ, Johnson R, Oxman MN, et al. The impact of herpes zoster and postherpetic neuralgia on health-related quality of life: a prospective study. CMAJ. 2010;182(16):1731–6.
24. Singhal PK, Makin C, Pellissier J, Sy L, White R, Saddier P. Work and productivity loss related to herpes zoster. J Med Econ. 2011;14(5):639–45.
25. Holbech JV, Bach FW, Finnerup NB, Jensen TS, Sindrup SH. Pain phenotype as a predictor for drug response in painful polyneuropathy-a retrospective analysis of data from controlled clinical trials. Pain. 2016;157(6):1305–13.
26. Oxman MN, Levin MJ, Johnson GR, Schmader KE, Straus SE, Gelb LD, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. N Engl J Med. 2005;352(22):2271–84.
27. Lal H, Cunningham AL, Godeaux O, Chlibek R, Diez-Domingo J, Hwang SJ, et al. Efficacy of an adjuvanted herpes zoster subunit vaccine in older adults. N Engl J Med. 2015;372(22):2087–96.