

REVIEW

# Real-World Effectiveness and Safety of a Live-Attenuated Herpes Zoster Vaccine: A Comprehensive Review

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## ABSTRACT

Herpes zoster (HZ) is a common, painful and debilitating disease caused by the reactivation of latent varicella-zoster virus in ganglia. This clinical event occurs more frequently in the elderly and those who are immunocompromised. The most common complication of HZ is post-herpetic neuralgia (PHN) which is responsible for the highest HZ-related burden of illness and is challenging to treat. Due to the important clinical and economic impact of HZ and PHN, and the suboptimal treatments that are currently available, HZ vaccination is an important approach to reduce the burden of illness. Currently, one-dose, live-attenuated vaccine is licensed in the United States and Europe to prevent HZ and it is included in some

national immunization programs. The clinical efficacy, safety and tolerability of the vaccine has been demonstrated in two large phase III clinical trials, involving more than 38,000 and 22,000 individuals aged  $\geq 60$  and 50–59 years, respectively. This comprehensive review summarizes the extensive “real-world” effectiveness and safety data from both immunocompetent and immunocompromised individuals. These data confirm those from the clinical trials, supporting the use of HZ vaccine in clinical practice and provide evidence that the current recommendations for immunocompromised individuals should be revised.

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**Keywords:** Herpes zoster; Infectious diseases; Post-herpetic neuralgia; Shingles; Vaccine; Vaccine effectiveness; Vaccine safety

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## INTRODUCTION

The varicella-zoster virus (VZV) is a DNA virus that belongs to the *Herpesviridae* family,

subfamily *Alphaherpesvirinae* [1, 2]. After primary infection with VZV, it remains dormant in the dorsal root or cranial nerve sensory ganglia. When reactivation occurs it causes herpes zoster (HZ), also known as shingles, usually characterized by a vesicular eruption with severe pain in a single dermatome segment [2–5].

The course of acute HZ episodes can be complicated by post-herpetic neuralgia (PHN), which is a painful and debilitating condition defined as a chronic neuropathic resilient pain that persists for 3 months or more from the initial onset of the rash [6, 7]. The risk of VZV reactivation increases with the decline of cell-mediated immunity, particularly due to the aging [3]. In addition, individuals who are immunocompromised due by certain diseases, such as hematologic malignancies and solid cancers have an increased risk for a higher incidence and severity of HZ and its neurologic and ophthalmologic complications and visceral dissemination [8–16]. The risk of HZ and its complications is also higher in patients with autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus, and Crohn's disease due to both the pathologic process and to their immunosuppressive treatments [17–24].

The annual incidence rates of HZ are similar across countries, ranging from 3 to 5 per 1000 people in North America, Europe and Asia–Pacific [25]. In all countries, HZ shows a similar age-specific epidemiologic pattern, with a steep increase in the incidence rate in those aged 50 years or more, with up to 8–12 HZ cases per 1000 persons in those aged 80 years or more [25]. Nearly 50% of individuals aged 85 years or more have experienced HZ [3].

The incidence of PHN also increases with age, ranging between 5% and about 30% in the

adult population and between 25% and 50% in adults aged 50 years or more [25].

Herpes zoster and PHN affect the health-related quality of life and induce a substantial economic burden [26]. PHN has been reported to have an impact on physical, psychological, functional and social aspects of patients' lives causing interference with daily activities. HZ and PHN cannot be managed satisfactorily with the currently available treatments and severe cases require extensive healthcare resources, particularly for specialist consultations, diagnostic examinations, and sometimes, hospitalization [27].

The live-attenuated HZ vaccine, Zostavax<sup>®</sup> (Merck Sharp & Dohme Corporation), was first licensed by the American Food and Drug Administration (FDA) in 2006 for the prevention of HZ in adults aged  $\geq 60$  years [28]. In the same year, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) authorized Zostavax for the prevention of both HZ and PHN [29]. In March 2011, the FDA extended the indication to include adults aged between 50 and 59 years [30]. Zostavax is currently the only HZ vaccine approved for use in the United States (US) and in Europe [29, 31]. After its licensure in the US, the Advisory Committee on Immunization Practices (ACIP) recommends the use of Zostavax for prevention of HZ and its complications among adults aged  $\geq 60$  years [32]. In this age group the vaccine is reimbursed by private health insurance or through public program.

Advisory Committee on Immunization Practices also considered the use of HZ vaccine among adults aged 50 through 59 years [30], but up to date declines to recommend the vaccine in this age group, citing shortages of Zostavax and limited data on long-term protection in this age group.

In Europe, Zostavax has been recommended and public funded in many countries, such as United Kingdom, Greece, France and some regions in Germany and Italy, according to different immunization strategies. In Austria, the HZ vaccine is recommended to adults aged  $\geq 50$  years, but it is not public funded. The results from two phase III clinical trials, which lead to licensure of the vaccine, demonstrated that Zostavax was safe, well-tolerated and effective in preventing HZ and PHN in adults aged  $\geq 50$  years [33, 34]. The efficacy of Zostavax was reported to be 51.3% [95% confidence interval (CI) 44.2; 57.6] and 66.5% (95% CI 47.5; 79.2) for preventing HZ and PHN, respectively, in adults aged  $\geq 60$  years in shingles prevention study (SPS; ClinicalTrials.gov identifier: NCT00007501) [32]. In the Zostavax Efficacy and Safety Trial (ZEST; ClinicalTrials.gov identifier: NCT00534248), its efficacy was 69.8% (95% CI 54.1; 80.6) for preventing HZ in adults aged 50–59 years [34].

Since the introduction of Zostavax in the US immunization program nearly 10 years ago, several effectiveness studies assessing the efficacy of HZ vaccine in a ‘real-life’ setting have been conducted in immunocompetent and immunocompromised individuals. Here we will summarize the results obtained in these effectiveness studies. This article is based on previously conducted studies, and does not involve any new studies of human or animal subjects performed by any of the authors.

## HZ VACCINE EFFECTIVENESS IN IMMUNOCOMPETENT SUBJECTS

Since licensure, the effectiveness of HZ vaccine has been assessed in three retrospective studies in immunocompetent subjects in the US

(Table 1) [35–37]. One of these analyzed data for 303,044 enrollees from the Kaiser Permanente Southern California (KPSC) health plan from January 2007 to December 2009 [35]. The results showed that the HZ vaccine significantly reduced the risk of HZ [vaccine effectiveness (VE): 55%; 95% CI 52%; 58%]; VE was similar in all age groups and for individuals with chronic diseases. The HZ vaccine also reduced the risks of ophthalmic HZ (VE: 63%; 95% CI 39%; 77%) and HZ-related hospitalizations (VE: 65%; 95% CI 49%; 76%).

Another large retrospective cohort study, conducted over the same period (January 2007 to December 2009) included 766,330 immunocompetent and immunosuppressed subjects aged  $\geq 65$  years enrolled in the Medicare program [36]. VE against HZ, adjusted for age, gender, race, immunosuppression, low income, and comorbidity, was 48% (95% CI 39%; 56%) for all subjects and 51% (95% CI 41%; 59%) for immunocompetent subjects. The study reported VE against PHN at 30 and 90 days as 62% (95% CI 37%; 77%) and 59% (95% CI 21%; 79%), respectively. The third study assessed the VE of the HZ vaccine among 176,078 vaccinated and 528,234 unvaccinated KPSC enrollees. A significant risk reduction for HZ was reported for vaccinated subjects (VE: 51%; 95% CI 50%; 53%). The effectiveness was confirmed for all age groups and in patients with chronic diseases, but unlike the previous study, the VE seemed to lower in those aged 60–69 years compared with those aged  $\geq 70$  years [37].

Four smaller studies were conducted in immunocompetent populations [38–41]. The risk of recurrent HZ did not significantly differ between vaccinated and unvaccinated individuals in a matched cohort study among elderly individuals aged  $\geq 60$  years who had had a recent episode of HZ [38]. Another study reported

**Table 1** Summary of the characteristics and results from three retrospective cohort (nested case–control) studies assessing the effectiveness of the live-attenuated herpes zoster vaccine, Zostavax, in immunocompetent subjects

Characteristics			Vaccine effectiveness, % (95% CI)					
Study ID	Study setting/period	Median follow-up, years	Population	Total/vaccinated subjects	Herpes zoster	Post-herpetic neuralgia	Ophthalmic zoster	Hospitalization for herpes zoster
Tseng et al. [35]	KPSC/ 2007–2009	1.6	Immunocompetent subjects aged ≥60 years	303,044/75,761	55 (52; 58)	NA	63 (39; 77)	65 (49; 76)
Langan et al. [36]	Medicare/ 2007–2009	1.6	Immunocompetent and immunocompromised subjects aged ≥65 years	766,330/29,785 <sup>a</sup> 625,409/24,392 <sup>b</sup>	48 (39; 56) <sup>a</sup> 51 (41; 59) <sup>b</sup>	62 (37; 77) <sup>c</sup> 59 (21; 79) <sup>d</sup>	NA	NA
Tseng et al. [37]	KPSC/ 2007–2014	Not reported	Immunocompetent subjects aged ≥60 years	704,312/176,078	51 (50; 53)	NA	NA	NA

KPSC Kaiser Permanente Southern California, CI confidence interval, NA not assessed

<sup>a</sup> Overall study population (immunocompetent and immunocompromised subjects)

<sup>b</sup> Only immunocompetent subjects

<sup>c</sup> Postherpetic neuralgia at 30 days

<sup>d</sup> Postherpetic neuralgia at 90 days

that the overall risk of PHN was significantly reduced in immunocompetent individuals aged  $\geq 60$  years who had developed HZ, after having received the HZ vaccine (VE: 41%; 95% CI 15%; 59%) [39]. Gender-specific analysis revealed that the risk reduction for PHN was predominately observed for women with no significant difference for men. It was suggested that this gender-related difference may reflect differences in healthcare-seeking patterns but this requires further investigation. The third study reported that the VE of the HZ vaccine for HZ in immunocompetent individuals was maintained also when the vaccine was administered concomitantly with polysaccharide pneumococcal vaccine compared with non-concomitant administration, with an adjusted hazard ratio of 1.19 (95% CI 0.81; 1.74) [40]. Another matched case–control study evaluated the VE of the HZ vaccine for preventing other HZ-related outcomes, such as prodromal symptoms and medically attended prodrome, as well as HZ and PHN [41]. In Southern Minnesota, US, 266 case-patients with HZ aged  $\geq 60$  years were matched with 362 controls from January 1, 2010 to October 12, 2011. The HZ vaccine significantly prevented HZ (VE: 54%; 95% CI 32%; 69%), HZ-related prodromal symptoms (VE: 58%; 95% CI 31%; 75%) and medically attended prodrome (VE: 70%; 95% CI 33%; 87%). The HZ vaccine also significantly reduced the risk of PHN at 30 days after rash onset (VE: 61%; 95% CI 22%; 80%) [41].

## HZ VACCINE DURATION OF PROTECTION IN IMMUNOCOMPETENT ADULTS

In clinical trials, the efficacy of HZ vaccine decreased over time. Indeed, the findings from short- and long-term persistence substudies, conducted, respectively, among 7320 vaccine

and 6950 placebo recipients and 6867 vaccinees enrolled in the SPS, demonstrated that vaccine efficacy steadily declined after vaccination but remained statistically significant for HZ burden of illness (BOI) through 10 years after vaccination. On the other hand, vaccine efficacy for incidence of HZ resulted statistically significant only until 8 years after immunization [42, 43].

Recently, Tseng and colleagues confirmed the reduction of HZ vaccine efficacy in the “real-world” [37]. In the above-mentioned study performed among KPSC members aged  $\geq 60$  years vaccinated against HZ between January 1, 2007 and December 31, 2014 and 528,234 unvaccinated subjects, they evaluated the persistency of HZ VE over 8 years after immunization. The VE in reducing the incidence of HZ was reported to decline gradually over time, with figures of 68.7% (95% CI 66.3%; 70.9%) during year 1 and 49.5% (95% CI 45.7%; 53.1%) during year 2; values ranging from 39.1% (95% CI 33.8–43.9%) to 32.9% (95% CI 23.1%; 41.5%) during years 3–6; and values of 16.5% (95% CI 1.4%; 29.3%) during year 7. Eight years after immunization, VE was 4.2% (95% CI –24.0%; 25.9%) and not statistically significant.

The reduction of protection against HZ and PHN with increasing time post-vaccination has been attributed to the declining levels of vaccine-induced immunity to VZV with increasing time after vaccination, as well as to weakening host immune responses due to the aging of vaccinated population [37, 43].

## HZ VACCINE EFFECTIVENESS IN IMMUNOCOMPROMISED ADULTS

Although the licensed HZ live-attenuated vaccine, Zostavax, has been shown to be safe and effective in older adults, it is currently not

recommended for use in patients with primary and acquired immunodeficiency because of its potential to trigger the development of HZ within 4–6 weeks after vaccination [15, 30, 44–48]. However, due to the high incidence and severity of HZ and its complications in patients with immunologic disorders, vaccination could potentially offer substantial benefits for these patients. Data from “real-world” studies provide evidence that the HZ vaccine could be effective and safe in patients with immunologic disorders (Table 2) [36, 49, 50]. In one study, HZ VE was assessed in 140,923 immunocompromised individuals among whom 5531 were vaccinated [36]. The incidence rates for HZ were higher in unvaccinated immunocompromised individuals compared with vaccinated individuals and VE against HZ was estimated to be 37% (95% CI 6%; 58%), providing support for the effectiveness of HZ vaccine in these at risk individuals [36]. A retrospective cohort study assessed HZ VE and safety in a large population of 463,541 Medicare beneficiaries aged  $\geq 60$  years who had selected immune-mediated diseases, using data from 2006 to 2009 (Table 2) [49]. Vaccination was not associated with a short-term increase in the risk for varicella or HZ and was found to be associated with a decrease risk of HZ with an estimated VE of 39% (95% CI 29%; 48%). In addition, they did not identify any safety signals in vaccinated patients undergoing biologic therapy within 42 days following vaccination. These findings confirmed the results of a previous smaller retrospective study involving 44,115 younger patients with the same immune-mediated diseases enrolled in a private healthcare insurance plan from 2006 to 2009. In this study, the short-term HZ incidence rates among the vaccinated and unvaccinated individuals were similar and no safety issues were reported [51].

In another study the incidence of HZ after immunosuppressive chemotherapy was compared in 4710 individuals aged  $\geq 60$  years who had been vaccinated with HZ vaccine before and in 16,766 individuals who had not (Table 2) [50]. There were 91 (cumulative incidence 3.3%) and 583 (cumulative incidence 5.3%) HZ cases among vaccinated and unvaccinated individual, respectively, within the 30 months follow-up period, resulting in an adjusted VE of 42% (95% CI 27%; 54%). This VE in immunocompromised patients was comparable to that reported for immunocompetent individuals evaluated in their previous study, 45% (95% CI 42%; 54%), suggesting that offering HZ vaccination to patients undergoing chemotherapy in a timely manner could offer substantial benefits [35].

## REAL-WORLD SAFETY OF HZ VACCINE

Since its licensure, the safety profile of the HZ vaccine has been investigated in large studies conducted in “real-world” settings. The results have been generally consistent with those reported in clinical trials, with no safety concerns detected, in both the general population and in certain patient groups with immune-mediated conditions. In one study, using data from the Vaccine Safety Datalink Project it was reported that the HZ vaccine is safe and well-tolerated in subjects aged  $\geq 50$  years, confirming pre-licensure results [52]. In addition, in this “real-world” setting, no increased risks for cerebrovascular, cardiovascular or neurological events were observed [52]. The optimal safety profile was also established: results from a large cohort study in about 29,000 vaccinated individuals aged  $\geq 60$  years enrolled in the Kaiser

**Table 2** Summary of the characteristics and results from three retrospective cohort studies assessing the effectiveness of the live-attenuated herpes zoster vaccine, Zostavax, in immunocompromised subjects

Characteristics				Results				
Study ID	Study setting/period	Median follow-up, days	Population	Total/vaccinated subjects	VCR, %	HZ incidence per 1000 person-years (95% CI)	VE against HZ, % (95% CI)	
				Vaccinated	Unvaccinated			
Zhang et al. [49]	Medicare/ 2006–2009	730	Individuals diagnosed with rheumatoid arthritis, psoriatic arthritis, psoriasis, ankylosing spondylitis or inflammatory bowel disease (Crohn's disease or ulcerative colitis) aged $\geq 60$ years	463,541/18,683	4.0	6.7 (5.7; 7.9)	11.6 (11.4; 11.9)	49 (29; 58) <sup>a</sup>
Langan et al. [36]	Medicare/ 2007–2009	584	Individuals with rheumatoid arthritis, inflammatory bowel disease aged $\geq 65$ years (34% aged $\geq 80$ years)	140,925/5531	2.3	5.4 (4.6; 6.4)	10.0 (9.8; 10.2)	37 (6; 58) <sup>b</sup>
Tseng et al. [50]	KPSC/ 2007–2012	730	Individuals who had received chemotherapy with myelosuppressive agents aged $\geq 60$ years	21,476/4710	21.9	12.9 (10.5; 15.8)	22.1 (20.3; 23.9)	42 (27; 54) <sup>a</sup>

KPSC Kaiser Permanente Southern California, CI confidence interval, VCR vaccine coverage rate, VE vaccine effectiveness

<sup>a</sup> Adjusted VE against HZ

<sup>b</sup> VE in immunosuppressed individuals

Permanente Northern California reported no short-term or long-term safety issues [53].

Recently, the results from a matched case–control study of events reported in the US Vaccine Adverse Event Reporting System (VAERS) demonstrated no significantly increased risk of exacerbation or induction of severe autoimmune diseases, including Guillain–Barre syndrome, multiple sclerosis, optic neuritis, systemic lupus erythematosus, thrombocytopenia or vasculitis, after vaccination [54]. However, HZ vaccine recipients were significantly more likely to develop alopecia or arthritis than recipients of tetanus toxoid-containing vaccines.

The HZ vaccine has been reported to be safe in two studies conducted among patients undergoing immunosuppressive treatments. In particular, no adverse reactions were reported in 62 patients with hematologic malignancy following the administration of the HZ vaccine [55]. Another study, conducted using data from 14,554 adults aged  $\geq 18$  years in the Vaccine Safety Datalink Project, reported a modest increased risk of HZ within the 42 days after immunization in current immunosuppressant drug users compared with previous immunosuppressant drugs users, thus supporting the current recommendations to withhold immunosuppressant treatment for 4 weeks before HZ vaccine administration [56]. Indeed, the study authors attributed this increased risk to the reactivation of VZV latent infection rather than vaccine viral strain dissemination.

## CONCLUSIONS

This comprehensive review has summarized available evidence for HZ VE and safety from studies with different designs, conducted in different populations in “real-world” settings.

This evidence confirms the promising impact of the HZ vaccine on the incidence of HZ and PHN observed in the pre-licensure clinical trials in “real-world” settings. In particular, the vaccine’s good safety and tolerability profiles have been confirmed in all available studies. Robust data show that the HZ vaccine can prevent HZ and PHN in immunocompetent individuals although the VE appears to decline with increasing age and time after vaccine administration, suggesting the need for a booster dose which is currently under discussion. Additionally, a single study has provided some evidence that the HZ vaccine may also be effective for the reduction of HZ-related hospitalizations and ophthalmic HZ. Nevertheless, more studies are needed to confirm these results. Although HZ vaccine use is currently contraindicated in immunocompromised individuals, available evidence suggests there may be a potential benefit of HZ vaccine in immunosuppressed patients and in individuals with selected immune-mediated diseases in this group with a good safety profile. Thus, there is evidence that the current recommendations in these populations should be reconsidered and revised. Overall, the “real-world” data summarized here provide a reassuring picture of the HZ vaccine performance during routine clinical practice.

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**Compliance with Ethics Guidelines.** This article is based on previously conducted studies, and does not involve any new studies of human or animal subjects performed by any of the authors.

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