

Background paper

# Herpes zoster vaccines

SAGE Working Group on Varicella and Herpes Zoster Vaccines

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## Background

Herpes zoster (HZ), commonly known as shingles, is caused by the reactivation of the varicella zoster virus (VZV). The clinical manifestation is a unilateral vesicular rash, characteristically restricted to a single dermatome, which is usually accompanied by radicular pain along that dermatome. Patients experience significant pain and discomfort that may last for weeks, months or even years in severe cases, diminishing the quality of life.

The VZV remains dormant inside multiple dorsal root ganglia after the initial varicella infection with the virus. Subclinical reactivation can occur intermittently in immune-compromised and immunocompetent individuals with detection of VZV DNA in the blood with consequent boosting in immunity (endogenous boosting)<sup>1</sup> or after exposure to varicella or HZ (exogenous boosting)<sup>2</sup>. Some studies have found that re-exposure to varicella-zoster virus or to children < 10 years is associated with a decreased risk of developing herpes zoster at a later stage in life,<sup>3, 4</sup> whereas other studies have not found this association.<sup>5, 6</sup> Clinical VZV reactivation (herpes zoster) occurs as result of a reduction in the level of T-cell immunity to VZV, a correlate of protection against herpes zoster, which is observed with increasing age.<sup>7</sup> Reactivation leads to ganglionitis with damaging of neurons and supporting cells followed by intense inflammatory response.<sup>8</sup> In 70-80% of herpes zoster cases, prodromal pain occurs, restricted to the affected dermatome. Vesicles appear for 3-4 days, followed by umbilication, ulceration and crusting of the lesions. The rash is accompanied by pain which may be severe.<sup>9</sup>

The most common serious complication of herpes zoster is postherpetic neuralgia (PHN), defined as pain that persists more than a defined period of time (90 days was used in the vaccine clinical trials), after onset of rash or after cutaneous healing.<sup>10</sup> About 20% of patients with herpes zoster will develop PHN. Age is the most important risk factor for development of PHN, with most cases occurring in adults over 40 years of age and adults over 70 years having a four times increased risk of PHN than those younger than 60 years.<sup>11, 12</sup>

Other serious complications of herpes zoster include blindness secondary to ophthalmic zoster, bacterial superinfections of zoster skin lesions and disseminated infections, which occurs more commonly in immunocompromised patients.<sup>13</sup> Based on limited available data from 366 mothers, herpes zoster during pregnancy does not appear to increase the risk of intrauterine infection in the unborn.<sup>14</sup> An increased risk of herpes zoster in infancy has been reported in children whose mothers had had varicella in pregnancy.<sup>15</sup>

Prompt antiviral therapy, if available, is recommended for herpes zoster in healthy and immunocompromised patients. Oral antiviral therapy should be commenced as early as possible, within 72 hours of rash onset. Treatment is usually given for 7 days in the absence of complications of herpes zoster. For immunocompromised persons who require hospitalization and in case of severe neurologic complications intravenous acyclovir is recommended. Management of acute pain associated with herpes zoster is complex. Non-steroidal anti-inflammatory drugs or in severe cases of severe pain, opioids may be used.<sup>16</sup>

Since a prerequisite for developing HZ is a past primary VZV infection, the epidemiology of varicella may also affect the epidemiology of HZ. There is some variation described in the epidemiology of VZV infection between temperate and tropical climates<sup>17-19</sup>. More than 90% of primary VZV infections in temperate climates occur before adolescence, in contrast to the tropics where a higher proportion of adults have not yet been infected with VZV<sup>18-21</sup>. However, available data on varicella incidence and seroprevalence that is representative and population-based, suggest that it is uncommon not to acquire varicella by 40-50 years of age even in the tropical countries though exceptions exist, especially in island populations such as Sri Lanka<sup>22, 23</sup>.

The incidence and severity of herpes zoster disease increase with age, with an exponential increase in incidence after the age of 50 years, which correlates with ageing-related decline in cell-mediated immunity.<sup>24</sup> Among adults aged 22 years and over, approximately 70% of HZ cases occur after 50 years of age<sup>25-27</sup>. Among adults who reach 85 years of age, it is estimated that approximately half will have suffered at least one episode of HZ<sup>28, 29</sup>. Studies in the US, Canada, Israel, Taiwan and Japan report age-adjusted HZ incidence in the total population ranging from 3.4 –5 per 1000 person years and 8 - 11 per 1000 person years over the age of 65<sup>12, 30, 31-34</sup>. The Israeli study also reported comparative incidence density rate for HZ of 3.46 per 1000 person-years in the total population and 12.8 per 1000 person-years in immune-compromised patients<sup>33</sup>. Australia reported HZ and PHN incidence rates among adults ≥ 50 years of 10/1,000 and 1.45/1,000 persons respectively<sup>35</sup>. A study of 27 countries in Europe showed HZ incidence varying by country from 2.0 to 4.6/1 000 person-years with no clearly observed geographic trend<sup>36</sup>. A recent population-based study from Korea showed an annual prevalence of HZ (measured by clinic visits) of 7.93-12.54 per 1000 population with a rapid increase in age prevalence after 45–49 years of age, reaching the highest incidence in individuals in their 70s<sup>37</sup>. In Taiwan, a study conducted between 2000 and 2006 showed that the incidence rate of HZ for all age groups was approximately 5 per 1000 person years<sup>34</sup> which is similar to rates described in temperate climates<sup>27, 38-40</sup>.

Surveillance activities to monitor the incidence of herpes zoster and assess the impact of varicella and zoster vaccination are more frequently reported from those countries having introduced one or both of these vaccines into routine childhood and/or adult immunization schedules<sup>41-44</sup>. There is scarcity of literature on VZV and HZ incidence in low and middle income countries. Most estimates of HZ incidence have been made in developed countries with temperate climates<sup>27, 38-40, 45</sup>. Where the burden of disease of VZV and HZ are compared, the burden of HZ is higher, mainly due to longer hospital stays<sup>46, 47</sup>. However, challenges with studying herpes zoster health burden, especially in elderly populations, include appropriate attribution of herpes zoster as the primary cause of severe morbidity or mortality rather than a contributing cause or a coincidental finding<sup>42</sup>.

Besides increase in age, immunosuppression from any cause, including hematologic malignancies, HIV and immunosuppressive medications, is an important risk factor for herpes zoster, increasing the risk of HZ by at least 10-fold<sup>48, 49</sup>. In developed countries, the lifetime risk of herpes zoster disease is approximately 30%<sup>27, 50</sup>. Considering the importance of age as a risk factor, life expectancy in populations would be expected to affect HZ incidence and total disease burden to a large degree. Race is

also a well described risk factor with the Black population in the US and the UK having a much lower incidence (about one fourth to a half) of HZ than the white population<sup>51, 52</sup>. Other identified risk factors include sex (most studies show a higher incidence among women irrespective of patterns of health seeking behavior) and stress or trauma, diabetes and higher social class<sup>33, 40</sup>.

Mathematical models that assume that external boosting plays an important role in maintaining VZV cell mediated immunity, and thereby delaying the onset of zoster in those who had primary VZV infection, predict that universal childhood varicella vaccination immunization programs will impact the incidence of herpes zoster, theoretically by reducing exposure to circulating wild virus and subsequent boosting<sup>53</sup>. Whilst an increase in herpes zoster incidence has been observed in the US and in other countries with childhood varicella vaccine programs<sup>11, 52</sup>, increasing trends have been noted in countries not using varicella vaccine universally in children<sup>11, 32, 37</sup>. Additionally, in the US, the trend precedes the introduction of universal varicella vaccination<sup>30, 44</sup> and the rate of increase in herpes zoster did not change in the pre and post vaccine time periods suggesting that other factors are affecting the increase.<sup>41, 44, 54, 55</sup> Studies continue to examine this issue and to explore what factors, including potentially vaccination, may be responsible for the increasing trend observed widely throughout the developed world.

A live attenuated herpes zoster vaccine, (Merck and Co., Inc) was first licensed in 2006 and is currently licensed in over 60 countries including those in the EU, US, Canada and Australia. This VZV vaccine contains an OKA derived varicella- zoster virus strain that is given in a single dose and administered subcutaneously. It is licensed for use in immunocompetent individuals 50 years and over by the European Medicines Agency (EMA), Australia's Therapeutic Goods Administration (TGA) and the U.S. Food and Drug Administration (FDA). Recommendations for routine vaccine administration by national policy setting groups, physicians associations or reimbursement agencies have been made in countries in Europe and Asia including Austria and Sweden ( $\geq 50$  years), the U.S., Canada, Greece, Korea and Thailand ( $\geq 60$  years), Australia (60-79 years) and the U.K. (70-79 years). This vaccine contains 19,400 plaque-forming units (PFU) and is similar in potency to one formulation of MMRV vaccine (ProQuad) and has an estimated 14 times higher potency than that of monovalent varicella vaccine guaranteed at expiration. Both lyophilized and refrigerator-stable vaccine formulations are licensed. The vaccine is contraindicated for people with a history of anaphylactic/anaphylactoid reaction to gelatin, neomycin, or any other component of the vaccine; with a history of primary or acquired immunodeficiency state, including leukemia, lymphoma, or other malignant neoplasm affecting the bone marrow or lymphatic system, or with acquired immunodeficiency syndrome or other clinical manifestation of infection with human immunodeficiency viruses; those receiving immunosuppressive therapy, including high-dose corticosteroids; or those who are or may be pregnant.

## Objectives

The Strategic Advisory Group of Experts on Immunisation (SAGE) Working Group on Herpes Zoster Vaccine (established in May 2012) was tasked with reviewing the evidence, identifying information gaps, and guiding the work required to address the information gaps and formulate proposed recommendations related to the use of herpes zoster vaccines in order to update the current 1998 varicella vaccine WHO position paper for SAGE review.

- 1) This report identifies, assembles and reviews published literature and available evidence related to main topics considered by the working group, including:
  - a) Data regarding the global prevalence and burden of disease caused by herpes zoster according to country development status
  - b) Issues related to herpes zoster surveillance
  - c) The safety, effectiveness and immunogenicity profile of herpes zoster vaccines and duration of protection following immunization
  - d) Impact of co-administration of herpes zoster vaccines with other vaccines
  - e) Evidence on the cost- effectiveness of different approaches to using the vaccine, in particular in low and low- middle income countries
- 2) The Working Group was asked to critically appraise this evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to rate the quality of evidence of key literatures on predefined research questions (PICO questions) as specified in the SAGE Guidance for the development of evidence-based vaccine related recommendations<sup>1</sup>.

## Methods

The working group was informed by an update of the 2012 Cochrane systematic literature review on herpes zoster vaccines<sup>56</sup>. The Cochrane literature review considered published, peer-reviewed literature as the primary source of data. Types of study designs included were: RCTs or quasi-randomized controlled trials. No restrictions were made to date of publication. References were retrieved from the following electronic databases: Cochrane Central Register of Controlled Trials (CENTRAL) [www.thecochranelibrary.com](http://www.thecochranelibrary.com) MEDLINE, EMBASE, LILACS and CINAHL. Start date was from the beginning of each candidate database up to September, 2013. Two reviewers independently screened titles and abstracts of all retrieved citations. Study authors and leading experts in the field of herpes zoster vaccines were contacted to provide additional information and identify associated published reports that relate to the subject.

PICO (Population, Intervention, Comparison and Outcome) questions were formulated by the working group. Population was either immunocompetent or immunocompromised adults. Outcomes of relevance for the working group to assess vaccine efficacy, safety and duration of protection following immunization were:

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<sup>1</sup>[http://www.who.int/immunization/sage/Guidelines\\_development\\_recommendations.pdf](http://www.who.int/immunization/sage/Guidelines_development_recommendations.pdf)

- all grades of severity of herpes zoster disease
- Post herpetic neuralgia (PHN)
- serious adverse events

Critical appraisal of evidence for the identified literature was done using the GRADE methodology. Evidence profiles summarizing the findings for each study question are provided in the Cochrane review.

## Results

### Vaccine efficacy and effectiveness

The pivotal clinical trial to assess pre-licensure efficacy and safety of Zostavax, the only licensed herpes zoster vaccine, was the Shingles Prevention Study, a randomized double-blinded placebo-controlled study initiated in November 1998, which enrolled 38,546 adults aged 60 years and over at 22 trial sites in the US. All vaccine and placebo recipients were actively followed for new cases of HZ through September 2003. The mean follow-up time was 3.13 years, 95% of enrolled participants completed the study, 1% were lost to follow up and 4% died in course of the study<sup>57</sup>. Less than 7% of subjects were aged 80 years of age or older, resulting in lower statistical power to evaluate the vaccine in this older age group. Herpes zoster cases were confirmed by PCR testing (93%), viral culture (1%), or evaluation by a panel of five physicians with expertise in zoster diagnosis (6%). Patients with confirmed herpes zoster were followed for at least 182 days to assess the outcome of the condition, including presence and severity of pain. The efficacy of herpes zoster vaccine in preventing herpes zoster disease as well as PHN and burden of zoster illness was evaluated. Reduced incidence of herpes zoster in the vaccine group was observed as early as 42 days following vaccination (RR: 0.29; 95%CI: 0.13-0.68). The overall vaccine efficacy against herpes zoster disease was 51.3% (5.42 cases/1000 person years vs 11.12cases/1000 person years;  $p < 0.001$ ).

The vaccine efficacy in preventing PHN was 66.5% (27 vs 80 cases;  $p < 0.001$ ) reflecting a significant reduction in the relative risk of PHN in the vaccinated group compared to the placebo group (RR: 0.34, 95%CI: 0.22-0.52). A burden of illness score for HZ (that incorporated the incidence, severity, and duration of pain and discomfort from HZ) was calculated, and efficacy against this outcome was 61.1% (95% CI 51.1-69.1).

In the Shingles Prevention Study, HZ vaccine efficacy against HZ decreased with age (from 64% among subjects aged 60–69 years to 38% among subjects aged 70 years). Vaccine efficacy against PHN remained constant with age (66% among subjects aged 60–69 years and 67% among subjects aged 70 years). An age-stratified analysis examined whether the HZ vaccine reduces the incidence of PHN beyond the reduction in PHN incidence provided by preventing herpes zoster. Results showed that, although there was no significant additional efficacy in preventing PHN in subjects aged 60–69 years, the vaccine efficacy in preventing PHN among subjects with herpes zoster who were aged 70 years and over was 49% ( $p = 0.01$ ). A burden of illness score for HZ (that incorporated the incidence, severity, and duration of pain and discomfort from HZ) was calculated, and efficacy against this outcome was 61% (95% CI 51-69).<sup>58</sup>

A subsequent RCT performed in 22,439 immunocompetent individuals aged 50–59 years in North America and Europe demonstrated vaccine efficacy of 69.8% (95% CI: 54.1–80.6) in preventing HZ. The incidence of herpes zoster was 1.99/1000 person-years in vaccinated vs 6.57/1000 person-years in the control group; (RR: 0.31 (95%CI: 0.2-0.5,  $p < 0.0001$ )<sup>59</sup> One small RCT powered to look at safety and immunogenicity compared a higher potency versus a lower potency formulation of herpes zoster vaccine and reported a non-significant higher risk for confirmed herpes zoster cases in the higher potency group (RR 2.55, 95% CI: 0.012-52.99).<sup>60</sup>

Post-licensure data examining risk of HZ in 76,000 vaccinated persons compared to 227,000 unvaccinated adults 60 years and older demonstrated that the vaccine was 55% effective (95% CI 52–58%) in preventing herpes zoster cases. The incidence of herpes zoster among vaccinated individuals was 6.4 per 1000 person-years; 95% CI: 5.9–6.8, and for unvaccinated individuals it was 13.0 per 1000 person-years; 95% CI: 12.6–13.3. In addition to overall reduction of herpes zoster cases, the vaccine was 63% effective in preventing ophthalmic herpes zoster and 65% effective in preventing hospitalizations coded as herpes zoster (VE 65%).<sup>61</sup>

### Concomitant administration of herpes zoster vaccines with other vaccines

Concomitant administration of herpes zoster vaccines with inactivated influenza vaccines in adults 50 and older has not demonstrated a reduced immunogenicity to either vaccine<sup>62</sup>. Although a study of simultaneous administration of HZ with pneumococcal polysaccharide vaccine demonstrated a significant reduction in VZV antibody when administered concomitantly,<sup>63</sup> a retrospective cohort study of more than 76,000 vaccine recipients demonstrated that the efficacy of herpes zoster vaccine was not affected by concomitant pneumococcal polysaccharide vaccine administration<sup>64</sup>.

### Duration of protection

Data on duration of protection following HZ are limited. In the Shingles Prevention Study, the median surveillance period for assessing vaccine effectiveness was 3.12 years.<sup>57</sup> Results from the Short-Term Persistence Study (STPS) indicate possible waning of protection against HZ overtime. The STPS was a phase 3, randomized, placebo-controlled, double-blind trial at 12 sites in the US. STPS re-enrolled 7320 vaccine and 6950 placebo recipients from the 38 546-subject SPS population and followed them to year 7 post-vaccination. Initially, reduction of HZ was significantly higher for the vaccinated group (RR: 0.53, 95%CI: 0.38-0.74). In the STPS as compared to the SPS, vaccine efficacy for herpes zoster burden of illness decreased from 61.1%(95%CI: 51.1–69.1) in the years 0.0–4.9 to 50.1%(95%CI: 14.1–71.0) in the years 3.3–7.8, vaccine efficacy for the incidence of PHN decreased from 66.5% (95%CI: 47.5–79.2) in the years 0.0–4.9 to 60.1%(95%CI: –9.8 to 86.7) in the years 3.3–7.8, and vaccine efficacy for the incidence of herpes zoster decreased from 51.3% (95%CI: 44.2–57.6) in the years 0.0–4.9 to 39.6%(95%CI: 18.2–55.5) in the years 3.3–7.8. The HZ burden of illness was defined as the sum of all of the HZ severity of illness scores using the Zoster Brief Pain Inventory in the respective randomization group divided by the person-years of observation.<sup>65</sup> Following completion of the STPS, the long-term persistence study (LTPS) evaluated the duration of protection against HZ, PHN and HZ BOI in a total of 6,867 subjects previously vaccinated with ZOSTAVAX in the SPS. The mean age at enrollment into the LTPS was 74.5 years and the

median follow-up period was ~3.9 years. A concurrent placebo control was not available in the LTPS; data from prior placebo recipients were used to estimate vaccine efficacy. The LTPS analyses for vaccine efficacy are based on data collected primarily from Year 7 through Year 10 following vaccination in the SPS. The estimated vaccine efficacy during the LTPS follow-up period was 21% (95% CI: [11 to 30%]) for HZ incidence, 35% (95% CI: [9 to 56%]) for PHN incidence and 37% (95% CI: [27 to 46%]) for HZ BOI<sup>66</sup>.

The quality of evidence was graded for following research questions.



## Efficacy of herpes zoster vaccination in immunocompetent adults (≥60 years)

**Population:** Immunocompetent adults (≥ 60 years)  
**Intervention:** Herpes zoster vaccination (single dose)  
**Comparison:** Placebo/no intervention  
**Outcome :** Cases of herpes zoster

What is the scientific evidence of the vaccine efficacy against herpes zoster conferred by one dose herpes zoster vaccination (versus placebo/no vaccination) in immunocompetent adults (≥60 years)?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		2/ RCT <sup>2</sup>	4
	Factors decreasing Confidence	Limitation in study design	None serious <sup>3</sup>	0
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	None Serious	0
		Publication bias	None serious	0
	Factors increasing Confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			4
Summary of Findings	Statement on quality of evidence			We are moderately confident in the estimate of effect on health outcome. The true effect is likely to be close to the estimate of the effect
	Conclusion			A single dose of herpes zoster vaccination is efficacious and effective to protect immunocompetent adults (≥60 years) against herpes zoster. A single dose of herpes zoster vaccination demonstrated vaccine efficacy of 51% to protect immunocompetent adults (≥60 years) against herpes zoster disease.

Reference List<sup>56, 57, 67, 68</sup>

Gagliardi AMZ, Silva BNG, Torloni MR, Soares BGO. Vaccines for preventing herpes zoster in older adults<sup>1</sup>. Cochrane Database of Systematic Reviews 2012;(10).

Langan SM, Smeeth L, Margolis DJ, Thomas SL. Herpes zoster vaccine effectiveness against incident herpes zoster and post-herpetic neuralgia in an older US population: a cohort study

1. PLoS Med 2013;10(4):e1001420.

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 Jun 2;352(22):2271-84.

<sup>2</sup> A Cochrane review (Gagliardi et al. 2012) identified one large RCT (Oxman et al. 2005) with low risk of bias addressing the research question. Risk ratio for 60-69 compared to placebo: 0.36 (95% CI: 0.3-0.45) and 0.63 (95% CI: 0.53-0.75) in adults over 70 years. Incidence per 1000 Person Years: 5.4 in participants who had received herpes zoster vaccine; 11.1 in participants who had received placebo. Vaccine efficacy: 51.4% (95%Confidence Interval 44.2-57.6%). Analyses according to age groups indicated a greater benefit in participants aged 60 to 69 years, RR 0.36 (95% CI 0.30 to 0.45) and in participants aged 70 years and over, RR 0.63 (95% CI 0.53 to 0.75). One cohort study (Langan et al. 2013) calculated vaccine effectiveness in persons 65 years and over to be 0.48 (95% CI:0.39–0.56) compared to unvaccinated individuals. Post-licensure data examining risk of HZ in 76,000 vaccinated persons compared to 227,000 unvaccinated adults 60 years and older demonstrated that the vaccine was 55% effective (95% CI 52-58%)in preventing herpes zoster cases (Tseng et al. 2011).

<sup>3</sup>Vaccine effectiveness over a longer period of time (>5 years) still needs to be assessed.

## **Efficacy of herpes zoster vaccination in preventing post-herpetic neuralgia (PHN) in immunocompetent adults (≥60 years) after herpes zoster vaccination**

**Population :** Immunocompetent adults (≥60 years)

**Intervention:** Herpes zoster vaccination

**Comparison:** Placebo/no intervention

**Outcome :** Post herpetic neuralgia (PHN)

<i>What is the scientific evidence of the vaccine efficacy against PHN conferred by one dose herpes zoster vaccination (versus placebo/no vaccination) in immunocompetent adults (≥60 years)?</i>				
			Rating	Adjustment to rating
<b>Quality Assessment</b>	No. of studies/starting rating		1/ RCT <sup>4</sup>	4
	Factors decreasing Confidence	Limitation in study design	None Serious	0
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	None Serious	0
		Publication bias	None serious	0
	Factors increasing Confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	<b>Final numerical rating of quality of evidence</b>			<b>4</b>
<b>Summary of Findings</b>	<b>Statement on quality of evidence</b>			<b>We are very confident that the true effect lies close to that of the estimate of effect on health outcome</b>
	<b>Conclusion</b>			<b>A single dose of herpes zoster vaccination is effective to protect Immunocompetent adults (≥60 years) against PHN. Individuals vaccinated with herpes zoster vaccine had a reduced risk ratio (0.34 (95% confidence interval: 0.22-0.52)) of developing PHN compared to unvaccinated individuals.</b>

Reference List<sup>57, 69</sup>

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 Jun 2;352(22):2271-84.

Chen N, Li Q, Zhang Y, Zhou M, Zhou D, He L. Vaccination for preventing postherpetic neuralgia. Cochrane Database of Systematic Reviews 2011;(3).

<sup>4</sup>A cochrane review (Chen et al. 2012) identified one RCT with low risk of bias (Oxman et al. 2005) with a total of 38.501 participants measuring incidence of PHN in vaccinated and participants receiving placebo. Risk ratio 0.34 (95% Confidence Intervall: 0.22-0.52).

## **Duration of protection in immunocompetent adults (≥60 years) after herpes zoster vaccination**

**Population :** Immunocompetent adults (≥60years)

**Intervention:** Herpes zoster vaccination

**Comparison:** Placebo/no intervention

**Outcome :** Duration of decreased herpes zoster incidence

<i>In immunocompetent adults (50+ years) what is the evidence for duration of decreased incidence of herpes zoster disease for any dose of herpes zoster vaccination compared to placebo?</i>			
		Rating	Adjustment to rating
<b>Quality Assessment</b>	No. of studies/starting rating		3/ RCT <sup>5</sup>
	Factors decreasing Confidence	Limitation in study design	Serious <sup>6</sup>
		Inconsistency	None serious
		Indirectness	Serious <sup>7</sup>
		Imprecision	None serious
		Publication bias	None serious
	Factors increasing Confidence	Large effect	Not applicable
		Dose-response	Not applicable
		Antagonistic bias and confounding	Not applicable
	<b>Final numerical rating of quality of evidence</b>		<b>2</b>
<b>Summary of Findings</b>	<b>Statement on quality of evidence</b>		<b>Our confidence in the estimate of the effect on the health outcome is limited</b>
	<b>Conclusion</b>		<b>The data is restricted to a seven year follow-up period, currently no data available on long-term duration of protection following herpes zoster vaccination.</b>

Reference List<sup>57, 65, 70</sup>

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 Jun 2;352(22):2271-84.

Levin MJ, Oxman MN, Zhang JH, Johnson GR, Stanley H, Hayward AR, et al. Varicella-zoster virus-specific immune responses in elderly recipients of a herpes zoster vaccine. J Infect Dis 2008 Mar 15;197(6):825-35.

Schmader KE, Oxman MN, Levin MJ, Johnson G, Zhang JH, Betts R, et al. Persistence of the efficacy of zoster vaccine in the shingles prevention study and the short-term persistence substudy 2. Clin Infect Dis 2012 Nov 15;55(10):1320-8.

<sup>5</sup> Levin et al. 2008: Follow-up of 1395 subjects after high-potency live attenuated Oka/Merck varicella-zoster vaccine. Immune responses from vaccine recipients vs placebo differed significantly three years after vaccination. Oxman et al. 2005: Cumulative incidence significantly lower in vaccine vs. placebo group. Schmader et al. 2012: Seven year follow up of 7,320 zoster vaccine recipients compared to 6,950 placebo controls: RR 0.54 (95%CI: 0.48-0.61) for cases of herpes zoster. Vaccine efficacy during the Long-term Persistence Substudy follow-up period (from year 7 through year 10 following vaccination in the Oxman 2005 study) was 21% (95% CI: 11 %to 30%) for HZ incidence.

<sup>6</sup> Follow up restricted to three years (Levin et al. 2008) and 7 years after receiving herpes zoster vaccine (Schmader et al.2012). Mean duration of follow up 3.1 years (Oxmann et al. 2005). No data available on longer periods.

<sup>7</sup> Immunology data used as correlate of protection (Levin et al.2008)

## Vaccine safety

Most studies on the safety of zoster vaccine relate to the licensed zoster vaccine, Zostavax. Zoster vaccine has been found to be safe in the SPS and a number of related and other RCTs, as well as in post-licensure safety studies. Among 38,500 subjects included in the SPS, the incidence of one or more serious adverse events 42 days post-vaccination was < 0.1% among vaccine and placebo groups<sup>57</sup>. In the more detailed vaccine adverse event sub-study<sup>65</sup>, the risk of serious adverse events within 42 days of vaccination was 1.9% in the vaccine group compared to 1.3% in the placebo group (risk difference: 0.7 (95%CI: 0.1 to 1.3)). Reported adverse events were varicella-like rash at injection site (0.1% vs 0.04%; risk difference: 0.07 (95% CI: 0.02 to 0.13)) and HZ like-rash (0.1% vs 0.2%; risk difference:-0.10 (95%CI:-0.18 to -0.03)). Adverse events at the injection site were significantly more common in the vaccine compared to placebo recipients (48.3% and 16.6%; risk difference 31.7, 95% CI: 28.3 – 32.6). The most common injection-site AE in the vaccine group included erythema, pain/tenderness and swelling. The mortality rate was equal (4.1%) in both vaccine and placebo groups<sup>57</sup>. Similar safety data were reported from other studies<sup>71</sup>.

Kerzner et al randomized HZ and flu vaccines given concomitantly or sequentially to adults 50 years and older and examined adverse events within 28 days of vaccination. Overall, a slightly higher proportion of subjects who received ZOSTAVAX concomitantly with influenza vaccine reported clinical AEs than did those in whom ZOSTAVAX was administered alone, although this difference was not statistically significant. Injection-site adverse events were the most frequently reported 44.7% vs 38.3% (concomitant vs nonconcomitant vaccination). Injection-site adverse events were more frequent in subjects aged 50-59 vs aged 60 and older (53.6% and 40.3%) and more common in concomitant than nonconcomitant group. Overall no serious vaccine-related AEs were reported in either group.<sup>72</sup>

MacIntyre et al conducted a randomized placebo-controlled trial in adults ≥ 60 years administering herpes zoster vaccine and pneumococcal polysaccharide vaccine either concomitantly or non-concomitantly. There was no significant difference in adverse events within 28 days of vaccination between arms.<sup>63</sup>

Gilderman et al compared refrigerated (n=182) vs frozen (n=185) formulations of herpes zoster vaccine in adults 50 years and older. Injection-site adverse events were reported in 35.6% vs 46.4% in refrigerated vs frozen formulation. No serious vaccine-related adverse events within 28 days of vaccination were observed in either study arms.<sup>73</sup>

In a two-dose herpes zoster vaccine study in adults ≥ 60 years, Vermeulen et al reported 49% vs 10.5% injection-site AEs in vaccine and placebo groups after the 1<sup>st</sup> dose, most commonly erythema, pain and swelling. Injection-site AEs were more frequent after the second dose of vaccine (49% vs 61.2%). No vaccine-related serious AEs within 42 days were reported in either group after 1<sup>st</sup> dose and 2<sup>nd</sup> dose of vaccine or placebo.<sup>74</sup>

Sutradharet al compared safety in two age-groups (50-59 years and ≥ 60years). No serious vaccine-related AEs were reported in either of the two arms. Injection-site adverse events (51% vs 34%) as well as systemic adverse events (5.8% vs 2.9%) were more common in the younger aged group.<sup>75</sup>

Mills et al evaluated the safety of herpes zoster vaccine for 28 days post-vaccination in 101 subjects  $\geq 50$  years with a prior history of HZ. A higher rate of injection-site adverse events was reported in the vaccine group compared to the placebo group (45.9% vs 4.2%). Systemic clinical adverse events were similar in both groups. No serious vaccine-related adverse events were reported in either arm.<sup>76</sup>

Post-licensure surveillance data is often better for evaluating rare adverse events, because the statistical power to detect such events may not be sufficient in RCTs. The best available post-licensure data come from a large US study which assessed the safety of zoster vaccine among 192,000 zoster vaccine recipients 60 years and older using the Vaccine Safety Datalink system. Various risk intervals (1–14, 15–28, 29–42 or 1–42 days) were studied post-vaccination and medical record reviews were conducted if needed. A significant increase in risk of allergic reactions was reported 1-7 days post vaccination (RR 2.32, 95%CI: 1.85–2.91) using a self-controlled case study design. The age-specific relative risk of allergic reaction (1-7 days) was approximately 3-4 times higher in the younger age group (50-59 years compared to 60 and over). Review of medical records showed that > 80% of the events involved a localized inflammatory response with redness, swelling and/or pain at the injection site (in varying degrees and combinations). The authors concluded that this reflected the coding of localized inflammatory responses using allergic-related codes. No increased risk of serious adverse events such as stroke, cardiovascular events, meningitis, encephalitis, encephalopathy, Ramsay-Hunt Syndrome or Bell's Palsy were identified within 42 days of vaccination.<sup>77</sup>

Another US post-licensure study with 29,010 study participants  $\geq 60$  years reported no significant increase in risk of acute myocardial infarction (RR: 1.29, 95% CI: 0.66–2.43; unadjusted p-value = 0.44), or stroke (RR: 0.91, 95% CI: 0.43–1.81; unadjusted p-value = 0.80) within 42 days of zoster vaccination. No vaccine-related deaths occurred within 42 days after receiving zoster vaccine.<sup>78</sup>

Recent safety studies related to investigational vaccines include one by Leroux-Roels 2012 who conducted a phase I/II, open-label, randomized, parallel-group trial that evaluated the safety and immunogenicity of a recombinant adjuvanted vaccine (HZ/su) in comparison with live attenuated varicella zoster virus vaccine (OKA) in healthy younger (18-30 years) and older adults (50-70 years). There were no reports of vaccine-related serious adverse events and no deaths.<sup>79</sup> This vaccine is now in a phase III clinical trial.

The quality of evidence was graded for following research questions.

## Safety of Herpes Zoster vaccine in immunocompetent adults ≥60 years

**Population:** Immunocompetent adults (>60 years)

**Intervention:** Herpes zoster vaccination

**Comparison:** Placebo/no intervention

**Outcome:** Serious adverse events

<i>In immunocompetent adults (60-69 years), what is the incidence of serious adverse events for any dose of herpes zoster vaccination compared to placebo?</i>				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		1/ RCT <sup>8</sup>	4
	Factors decreasing confidence	Limitation in study design	None Serious	0
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	None Serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			4
Summary of Findings	Statement on quality of evidence			We are very confident that the true effect lies close to that of the estimate of effect on health outcome
	Conclusion			Our confidence in the estimate of the effect is high that incidence of serious adverse events following one dose of herpes zoster vaccination in immunocompetent adults (>60 years) compared to placebo is low. Overall few reports and low incidence of serious adverse events in one RCT.

Reference List<sup>56, 57</sup>

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 Jun 2;352(22):2271-84.

Gagliardi AMZ, Silva BNG, Torloni MR, Soares BGO. Vaccines for preventing herpes zoster in older adults 1. Cochrane Database of Systematic Reviews 2012;(10).

<sup>8</sup>A Cochrane review (Gagliardi et al. 2012) calculated the risk ratio for serious adverse effects in vaccinees compared to placebo in participants 60-69 years: 1.2 (95% confidence interval (CI): 0.92-1.57) based on data from Oxman et al. 2005, a RCT with low risk of bias and >17 000 study participants.

## Herpes zoster vaccination in immunocompromised

Live HZ vaccine is contra-indicated in persons who are immunosuppressed from any cause, whether acquired, congenital, iatrogenic or disease-based. The safety and effectiveness of HZ vaccination in immunocompromised persons has been assessed in few post-licensure studies<sup>80-84</sup>. Zhang et al evaluated the incidence of herpes zoster in 463 541 Medicare beneficiaries with autoimmune diseases (rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis, or inflammatory bowel disease) 50 years and over with and without immunosuppressive therapy. There was no significant difference in age- and sex-adjusted herpes zoster incidence rates between patients who had received herpes zoster vaccine and persons who had not been vaccinated however the study only included 551 vaccine recipients in whom 5 cases of herpes zoster developed. The authors claimed that no significant increase in serious AEs was observed however no details were provided on the safety assessment. Naidus et al assessed safety in a small study of 62 patients  $\geq 50$  years with hematologic malignancies and hematopoietic cell transplant; 25% of whom concurrently received antiviral prophylaxis at the time of and/or beyond the date of vaccination. Participants were selected based on clinical impression of intact immunity. No vaccine-related AEs were reported. One patient developed trigeminal herpes zoster 3 weeks after vaccination but strain identification was not obtained. Parrino et al conducted a RCT with 300 subjects  $\geq 60$  years on long-term chronic/maintenance systemic corticosteroid therapy (daily dose equivalent of 5 to 20 mg prednisone). Compared to placebo, zoster vaccine was demonstrated to be immunogenic 6-weeks post vaccination and no increase in serious AEs was reported through 182 days post vaccination. Chakravarty et al estimated the immunogenicity and safety of HZ vaccination in a small pilot study of 10 female patients with mild Systemic Lupus Erythematosus (SLE) taking mild-moderate immunosuppressive medications and ten control subjects<sup>80</sup>. Limitations of the study were small number of participants, mild SLE disease as well as restricted immunosuppressive therapy. No episodes of HZ, vesicular rash, serious adverse events or SLE flare were reported. The proportion of subjects with a  $> 50\%$  increase in ELISPOT results following vaccination was comparable between both groups, although absolute SLE responses were lower than controls. Antibody titers increased only among controls following vaccination ( $p < 0.05$ ).

A randomized, double-blind, placebo-controlled trial assessed immunogenicity and safety of live attenuated HZ vaccine in VZV seropositive HIV-infected adults  $\geq 18$  years ( $CD4 > 200$  copies/ $\mu$ L; HIV RNA  $< 75$  copies/mL for  $\geq 6$  months on stable antiretroviral therapy [ART]). Primary safety endpoints were defined by the International Conference on Harmonization defined serious adverse events or NIAID grade 3 (of 4) signs/symptoms during 6-week post-vaccination periods. These endpoints were observed in 5.1% of 295 adults who received zoster vaccine and 2.1% of 97 adults who received placebo ( $p = 0.26$ ). Fever and rash were similar between the two groups and injection site reactions were more common in vaccine compared to placebo recipients (42.0% vs 12.4% respectively). The authors concluded that the vaccine was generally safe in HIV+ adults virologically suppressed on ART<sup>85</sup>.

## Cost- effectiveness of herpes zoster vaccination

One systematic review was conducted which took into consideration 11 studies from Europe and North America<sup>86</sup>. All studies except one provided consistent results and considered zoster vaccination to be

cost-effective in regard to gained quality-adjusted life years (QALY) when the vaccine is given at about 65-70 years of age, and if vaccine protection against PHN is longer than 10-15 years. The quality of evidence is generally good according to the BMJ criteria yet indirect as all results derive from modeling studies. Uncertainties remain in regard to the duration of vaccine protection as recent trial results indicate possible waning of protection<sup>59</sup>. Furthermore, cost-effectiveness data stems from high income countries- data on cost-effectiveness from low and middle-income countries is currently not available.

## Conclusions and recommendations

Epidemiological data on the burden of disease is available from selected high and medium income countries. Data from more medium income countries are needed. Data from low income countries are lacking including the effect of life expectancy, HIV prevalence and availability of treatment, race and other factors. The impact of large-scale varicella vaccination programs on the impact of herpes zoster incidence warrants continued surveillance. Although an increase in HZ incidence has been observed in countries with universal VZV vaccination programs such as the US and Australia, the increase precedes the commencement of the vaccination programs and an increase has been observed in countries without childhood varicella vaccination programs. The contributing factors to the observed increase are probably multifactorial, and are not yet well understood.

Herpes zoster vaccine efficacy and safety were assessed in large clinical trials and post-licensure surveillance data from high-income countries. The vaccine is safe and demonstrated clinical protection against herpes zoster, post-herpetic neuralgia and other serious herpes zoster complications.

To date no data are available on long term protection induced by the vaccine. Available data shows short term protection and waning of immunity. Assuming long-term protection (10-15 years), which appears now to be an unlikely scenario given the data cited above, modeling demonstrated the vaccine to be cost-effective in high-income countries. No data on cost-effectiveness is available from low- and middle-income countries.

Due to limited data and the unknown burden of disease in most countries, initial evidence of waning of protection over time and uncertainty of the optimal age for vaccination and the potential role of a booster dose, the working group cannot make any recommendation about routine herpes zoster vaccination at this time. However, some countries may decide to introduce vaccination if they have an important burden of disease and consider the program beneficial. Countries with an aging population and demographic shift towards older ages can also consider introduction of herpes zoster vaccination.

For those countries deciding to proceed with a herpes zoster vaccination program, the optimal age and dosing schedule of herpes zoster vaccination should take into consideration effectiveness, efficacy of booster doses, age-dependent burden of disease, cost-effectiveness and duration of vaccine protection.



**High priority research questions:**

Disease burden studies in low- and middle-income countries.

Duration of vaccine protection against HZ and severe complications (PHN, other).

Safety and efficacy of investigational vaccines in immunocompromised patients such as those with HIV.

Cost-effectiveness of herpes zoster vaccine in immunocompetent and immunocompromised populations, especially in low and middle income countries.

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