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# Preventing herpes zoster through vaccination: New developments

## ABSTRACT

Herpes zoster (HZ) affects 1 million Americans every year. The disease burden is higher in immunocompromised patients. The live-attenuated HZ vaccine is effective in preventing HZ and postherpetic neuralgia and has been recommended for immunocompetent adults age 60 and older. However, because protection wanes by 10 years, a booster may be necessary. In 2015, an adjuvanted subunit HZ vaccine was shown to reduce incidence by 97%, even in the elderly, but long-term data on vaccine protection are not available. Clinical trials are under way to investigate a safe and effective vaccine for immunocompromised patients.

## KEY POINTS

HZ continues to be an important public health problem, with substantial morbidity and economic impact. Because of the lack of effective treatment, vaccination provides the best strategy for disease mitigation.

Physicians can reduce the impact of HZ by educating patients about its complications and recommending immunization for all patients age 60 and older. Patients can protect themselves by seeking vaccination.

Vaccine protection wanes completely after 10 years, and physicians should be prepared to offer a booster dose should the Advisory Committee on Immunization Practices issue such recommendations.

Newer vaccines offer promise for greater efficacy, especially for the elderly. For immunocompromised patients, a safe and effective vaccine may be available in the near future.

**H**ERPES ZOSTER (HZ), or shingles, represents a reactivation of the varicella-zoster virus (VZV). Following primary infection, usually in childhood, the virus typically lies dormant in the dorsal root and sensory nerve ganglia for decades. The precise mechanism of reactivation is not well understood, but it is associated with a decline in cell-mediated immunity that occurs with advancing age, immune-compromising conditions such as HIV infection and cancer, or immunosuppressive therapies, including corticosteroids.<sup>1</sup> HZ is usually a self-limited disease characterized by unilateral dermatomal rash and pain, but can cause disseminated infection in immunocompromised individuals.<sup>2</sup>

Treatment with antiviral medications within 72 hours of rash onset can reduce acute HZ symptoms.<sup>1</sup> However, antiviral agents are only minimally effective in preventing postherpetic neuralgia, the most common complication of HZ.<sup>3</sup> Therefore, efforts to reduce the burden of HZ morbidity have focused on prevention through vaccination.

Currently, the only shingles vaccine approved by the US Food and Drug Administration (FDA) is Zostavax (Merck), which contains the live-attenuated Oka strain of VZV at a concentration 14 times greater than that of the varicella vaccine (Varivax, Merck). The live-attenuated vaccine boosts VZV-specific cell-mediated immunity, preventing reactivation of the latent virus.

In this article, we describe the burden of disease and review recent developments in the literature on HZ vaccine, including duration of efficacy, uptake and barriers to vaccination, cost-effectiveness, and the outlook for future vaccines.

## INCIDENCE INCREASES WITH AGE

The incidence of herpes zoster in the general population is between 3 and 5 per 1,000 person-years<sup>4</sup> and increases with age, especially after age 60 when the incidence can approach 13 to 15 per 1,000 person-years.<sup>5,6</sup> An estimated 1 million new cases occur each year in the United States, and about 6% of patients experience a second episode of HZ within 8 years.<sup>7,8</sup> In immunocompromised patients, the incidence of HZ is 2 to 10 times higher than in the general population.<sup>9</sup>

The incidence of HZ has been increasing for reasons that are unclear. After varicella vaccine was introduced into the routine childhood immunization schedule in 1995, it was hypothesized that the resultant decrease in primary varicella infections would remove a natural source of immune boosting and cause an increase in HZ incidence for up to 20 years.<sup>10</sup> However, recent studies demonstrate that the observed increase in HZ incidence actually predates the introduction of varicella vaccine,<sup>11–13</sup> and the widespread use of varicella vaccine has not resulted in an increase in the incidence of HZ.<sup>14</sup>

Other potential explanations for the rise in reported incidence include increasing awareness among patients, who might previously not have sought care and among physicians, who may be more likely to make the diagnosis. Advertisement of new treatments for HZ, including gabapentin and capsaicin, probably began to increase awareness in the 1990s, as did promotion of the HZ vaccine after its licensure in 2006.

HZ can occur in people who have been vaccinated against varicella due to reactivation of the vaccine-strain virus, but the risk is lower than after infection with wild-type varicella.<sup>15</sup> Given that the varicella vaccine has been routinely used in children for only 20 years, the long-term effect of varicella vaccination on the incidence of HZ in elderly people is unknown.

### Serious complications

HZ can cause rare but serious complications including encephalitis, herpes ophthalmicus, herpes oticus, myelitis, and retinitis.<sup>1</sup> These can lead to long-term disability including unilateral blindness and deafness.

The most common and debilitating complication is postherpetic neuralgia, a persistent pain lasting at least 3 months, with a mean duration of 3.3 years and sometimes as long as 10 years.<sup>16</sup> Postherpetic neuralgia occurs in 8% to 32% of patients after acute HZ,<sup>4</sup> and the incidence increases with age, being most common after age 70. The chronic pain of postherpetic neuralgia has a significant adverse impact on patients' quality of life, including physical disability and emotional distress.<sup>17</sup> Some pain is intense, and anecdotal reports of patients committing suicide were included in the Advisory Committee on Immunization Practices (ACIP) recommendations regarding herpes zoster vaccine.<sup>18</sup>

HZ and its complications also impose a substantial economic burden on society.<sup>19</sup> In a population-based study, the mean direct medical costs of HZ ranged from \$620 to \$1,160 (2015 dollars) depending on age,<sup>20</sup> and the mean costs of postherpetic neuralgia were 2 to 5 times higher than that.<sup>20–22</sup> Immunocompromised patients had costs 2 to 3 times higher than those of immunocompetent adults.<sup>23</sup> In addition, for employed patients, HZ resulted in an average loss of 32 hours of work due to absenteeism and 84 hours due to presenteeism (ie, working while sick and therefore suboptimally).<sup>24</sup>

Assuming there are 1 million cases of HZ each year, if 8% to 32% of patients go on to develop postherpetic neuralgia, that would translate into approximately \$1 to \$2 billion in direct medical costs. With 60% of adult patients working,<sup>25</sup> at an average wage of \$23.23 per hour,<sup>26</sup> HZ illness could be responsible for another \$1.6 billion in lost productivity.

## EFFICACY AND SAFETY OF HZ VACCINE

In 2006, the FDA approved the live-attenuated Oka strain VZV vaccine for prevention of HZ and postherpetic neuralgia in adults age 60 and older based on findings from the Shingles Prevention Study (SPS).<sup>27</sup>

### The Shingles Prevention Study

This multicenter randomized placebo-controlled trial<sup>27</sup> enrolled 38,546 immunocompetent persons age 60 and older. Subjects in the intervention group received a single dose of live-attenuated vaccine, and all participants were

The incidence of HZ has been increasing for reasons that are not clear

TABLE 1

## Clinical trials of herpes zoster (HZ) vaccines

	<b>Shingles Prevention Study (SPS)<sup>27</sup></b>	<b>Short-Term Persistence Substudy<sup>30</sup></b>	<b>Long-Term Persistence Substudy<sup>31</sup></b>	<b>Zostavax Efficacy and Safety Trial<sup>33</sup></b>	<b>ZOE-50<sup>53</sup></b>
<b>Intervention</b>	0.5 mL of the live-attenuated Oka/Merck VZV vaccine or placebo, subcutaneously	None	None	0.65 mL of the live-attenuated Oka/Merck VZV vaccine or placebo, subcutaneously	0.5 mL of recombinant VZV glycoprotein E and the AS01 <sub>B</sub> adjuvant system or placebo, intramuscularly
<b>Number of injections</b>	1			1	2, 2 months apart
<b>Number of participants</b>	38,546	14,270 SPS participants	6,867 SPS participants from the vaccine group	22,439	16,160
<b>Age, years</b>	69 (median)	73.3 (mean)	74.5 (mean)	54.9 (mean)	62.3 (mean)
<b>Mean duration of follow-up</b>	3.13 years	Placebo: 0.98 years Vaccine: 1.36 years	3.74 years	1.3 years	3.2 years
<b>Efficacy against HZ incidence</b>	51.3% <sup>a</sup>	39.6% <sup>a</sup>	21.1% <sup>a</sup>	69.8% <sup>a</sup>	97.2% <sup>a</sup>
<b>Efficacy against burden of illness</b>	61.1% <sup>a</sup>	50.1% <sup>a</sup>	37.3% <sup>a</sup>	Not reported	Not reported
<b>Efficacy against postherpetic neuralgia incidence</b>	66.5% <sup>a</sup>	60.1%	35.4 <sup>a</sup>	Not reported	Not reported
<b>Injection-site adverse events</b>	Placebo: 17% Vaccine: 48% <sup>a</sup>	Not applicable	Not applicable	Placebo: 14.4% Vaccine: 63.9% <sup>a</sup>	Placebo: 12% Vaccine: 82% <sup>a</sup>
<b>Serious adverse events</b>	Placebo: 1.3% Vaccine: 1.9% <sup>a</sup>	Not applicable	Not applicable	Placebo: 0.5% Vaccine: 0.6%	Placebo: 8.9% Vaccine: 9.0%

<sup>a</sup> Statistically significant.

ZOE-50 = Zoster Efficacy Study in Adults 50 Years of Age or Older

followed for up to 4.9 years after vaccination.

HZ occurred in 315 (1.636%) of the 19,254 participants in the vaccine group and in 642 (3.336%) of the 19,247 participants in the placebo group, an absolute risk reduction of 1.7%, number needed to treat 59, relative risk reduction 51%,  $P < .001$ . Similarly, postherpetic neuralgia occurred in 27 (0.140%) of the 19,254 vaccine recipients and in 80 (0.416%) of the placebo recipients (an absolute risk re-

duction of 0.276%, number needed to treat 362, relative risk reduction 66%,  $P < .001$ ). The investigators calculated that vaccination reduced the overall burden of illness by 61% (Table 1).

The efficacy against HZ incidence decreased with age,<sup>28</sup> but the efficacy against postherpetic neuralgia did not. In addition, vaccine recipients who developed HZ generally had less severe manifestations.

The safety of the vaccine was assessed for all participants in the SPS. In addition, one-sixth of SPS participants were enrolled in a safety substudy. These participants completed a detailed report card regarding all medically important events within the first 42 days. Forty-eight percent of the vaccine group and 17% of the placebo group ( $P < .05$ ) experienced adverse events, primarily at the injection site. Less than 1% of all local reactions were severe.<sup>29</sup> Serious adverse events were rare ( $< 2\%$ ), but occurred significantly more often in the vaccinated group.

### Short-Term Persistence Substudy

Short-term efficacy of the live-attenuated vaccine (up to 7 years) was assessed in the Short-Term Persistence Substudy (STPS), which involved 14,270 of the initial participants and reported yearly and overall vaccine efficacy.<sup>30</sup> After 5 years, the yearly efficacy against postherpetic neuralgia incidence declined to 32% and was no longer statistically significant. Efficacy against HZ incidence and burden of illness displayed the same pattern. After the end of the STPS, all subjects in the placebo group received vaccination.

### Long-Term Persistence Substudy

Those in the intervention group were followed for an additional 4 years in the Long-Term Persistence Substudy (LTPS).<sup>31</sup> Due to the lack of concurrent controls in the LTPS, the authors used regression models based on historical controls to estimate contemporary population incidence of HZ and postherpetic neuralgia for comparison.

Efficacy continued to decline over time, and by 10 years after vaccination there was no difference between vaccinated patients and historical controls in the rate of any end point (ie, efficacy declined to zero).

### A trial of booster vaccination

Because many patients are vaccinated at age 60, waning immunity could leave them vulnerable to HZ and postherpetic neuralgia by age 70. A potential solution would be to give a booster dose after 10 years.

A recent phase 3 clinical trial of adults age 70 years and older found that a booster dose of live-attenuated vaccine was as safe and immunogenic as an initial dose.<sup>32</sup> While antibody

responses were similar in the boosted group and the newly vaccinated group, cell-mediated immunity was higher in the boosted group.

Because prevention of HZ is generally via cell-mediated immunity, the booster might be more effective than the initial vaccination, but clinical trials measuring actual cases prevented will be required to prove it. A booster dose is not currently recommended.

### A trial of vaccination in adults 50 to 59

In 2011, the FDA extended its approval of HZ vaccine for use in adults ages 50 to 59.<sup>33</sup>

In a randomized, double-blind, placebo-controlled trial in this age group,<sup>33</sup> the vaccine reduced HZ incidence by almost 70% (absolute risk reduction 0.614%, number needed to treat 156; **Table 1**), but the severity of HZ cases was not affected. There were too few cases of postherpetic neuralgia to assess the efficacy for this end point. The study followed patients for only 1.5 years after vaccination, so the duration of efficacy is unknown.

As in the older recipients, the vaccine was well tolerated; injection-site reactions and headache were the major adverse effects reported among vaccine recipients.<sup>33</sup>

## ■ INDICATIONS AND CONTRAINDICATIONS

Although HZ vaccine is licensed for use in adults age 50 and older, the ACIP recommends it only for immunocompetent adults age 60 and older. At this time, the ACIP does not recommend HZ vaccine in those younger than 60 because of the low risk of HZ in this age group.<sup>34</sup>

Any person age 60 or older should receive a single dose of the live-attenuated HZ vaccine subcutaneously, regardless of past history of HZ.

The vaccine is contraindicated in patients who have a history of allergic reaction to any vaccine component, immunosuppression or immunodeficiency conditions, and pregnancy. Specifically, people who will receive immunosuppressive therapies should have the vaccine at least 14 days before beginning treatment. Antiviral medications such as acyclovir, famciclovir, and valacyclovir should be discontinued at least 24 hours before vaccination and not resumed until 14 days later. Patients taking high-dose corticosteroids for more than 2

**A booster dose is not currently recommended**

weeks should not be vaccinated until at least 1 month after therapy is completed.

In contrast, HZ vaccine is not contraindicated for leukemia patients who are in remission and who have not received chemotherapy or radiation for at least 3 months, or for patients receiving short-term, low-to-moderate dose, topical, intra-articular, bursal, or tendon injections of corticosteroids. Patients on low-dose methotrexate, azathioprine, or 6-mercaptopurine can also receive the vaccine.<sup>18</sup>

### ■ VACCINATION RATES ARE LOW

Although the vaccine has been recommended since 2008, uptake has been slow. **Figure 1** shows the rate of HZ vaccination in adults age 60 and older surveyed in the National Health Interview Survey from 2007 to 2013.<sup>35</sup> Eight years after the vaccine was licensed, only 28% of eligible patients had been vaccinated. Assuming the current rate of increase remains constant, it will take 7 more years to reach a 60% coverage rate—the same as for pneumococcal vaccine<sup>36</sup>—and 18 years to reach universal coverage.

### Barriers to vaccination

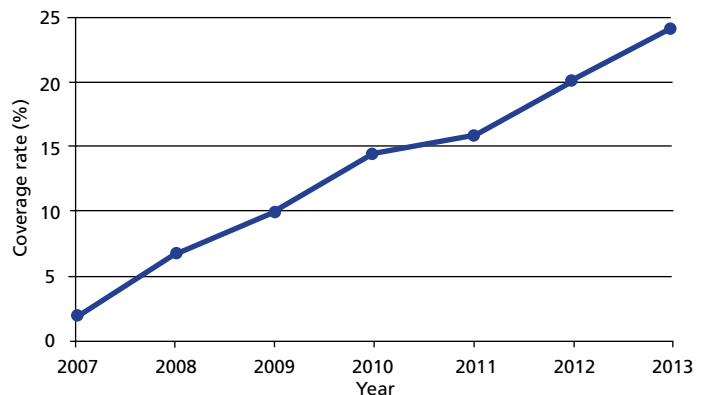
Several barriers to HZ vaccination might account for the slow uptake.

For the first few years the vaccine was available, the requirement to store it frozen presented an obstacle for some physicians.<sup>37</sup> Physicians may also have been discouraged by the cumbersome Medicare reimbursement process because while the administration fee is covered through Medicare Part B, the live-attenuated vaccine is reimbursed only through Medicare Part D, a benefit that varies by plans. Other barriers to physicians are supply shortages, high up-front costs, and uncertainties regarding the duration of vaccine protection, its safety, and side effects.<sup>38–40</sup>

Patient barriers include lack of physician recommendation, lack of familiarity with the vaccine, high out-of-pocket costs, the perception that they are at low risk for HZ, underestimation of the pain associated with HZ and postherpetic neuralgia, and fear of vaccine adverse effects.<sup>39,41,42</sup>

### Interventions to increase vaccination rates

Certain interventions have been shown to increase vaccination adherence in general and



**FIGURE 1.** Rates of vaccination against herpes zoster in adults age 60 and older between 2007 and 2013.

Data from Centers for Disease Control and Prevention (CDC). National Health Interview Survey. [www.cdc.gov/nchs/nhis/about\\_nhis.htm](http://www.cdc.gov/nchs/nhis/about_nhis.htm).

HZ vaccination in particular. In randomized trials involving other vaccines, electronic medical record reminders supporting panel management or nurse-initiated protocols have been proven to increase vaccination rates, but these methods have not been tested for HZ vaccine specifically.<sup>43,44</sup>

In an observational study, Chaudhry et al found that the number of HZ vaccinations administered at the Mayo Clinic increased 43% in one practice and 54% in another after the implementation of an electronic alert.<sup>45</sup> A randomized controlled trial showed that an informational package discussing HZ and the vaccine sent to patients via either their electronic personal health record or traditional mail increased HZ vaccination by almost 3 times.<sup>46</sup>

Pharmacists can also influence vaccination rates. States that provide full immunization privileges to pharmacists have vaccination rates significantly higher than states with restricted or no authorization.<sup>47</sup>

### ■ COST-EFFECTIVENESS CONSIDERATIONS

Unlike the Centers for Medicare and Medicaid Services, the ACIP does consider cost-effectiveness in their vaccine recommendations. Because of the morbidity associated with HZ and postherpetic neuralgia as well as the economic impact, vaccination is generally considered cost-effective for adults age 60 and older.<sup>48,49</sup>

Analyses have demonstrated that cost-effectiveness hinges on 4 factors: initial vaccine efficacy, the duration of efficacy, the age-specific incidence of HZ, and the cost of the vaccine.

**Adults age 60 and older should receive a single dose of the live-attenuated HZ vaccine**



For patients ages 50 to 59, the incidence of HZ is low, and because the duration of vaccine efficacy is short even though initial vaccine efficacy is high, vaccination in this age group offers poor value.<sup>50</sup> At older ages, the incidence of HZ and postherpetic neuralgia rises, making vaccination more cost-effective. After age 60, the vaccine is cost-effective at all ages, although age 70 appears to offer the optimal trade-off between increasing incidence and declining vaccine efficacy.<sup>48,49</sup>

For patients who plan to be vaccinated only once, waiting until age 70 would appear to offer the best value.<sup>51</sup> For those who are willing to receive a booster dose, the optimal age for vaccination is unknown, but will likely depend on the effectiveness, cost, and duration of the booster.

### ■ A NEW HZ VACCINE

In 2015, GlaxoSmithKline tested a new HZ vaccine containing a single VZV glycoprotein in an AS01<sub>B</sub> adjuvant system (HZ/su vaccine).<sup>52</sup> In a phase 3 randomized trial involving 15,411 immunocompetent persons age 50 and older, a 2-dose schedule of HZ/su vaccine was 97% effective in preventing HZ (Table 1).<sup>53</sup> Importantly, the vaccine was equally effective in older patients.

This vaccine also had a high rate of adverse reactions, with 17% of vaccine recipients vs 3% of placebo recipients reporting events that prevented normal everyday activities for at least 1 day. However, the rate of serious adverse reactions was the same in both groups (9%). The company announced that they intended to submit a regulatory application for HZ/su vaccine in the second half of 2016.<sup>54</sup>

Because of its high efficacy, HZ/su vaccine has the potential to change practice, but several issues must be resolved before it can supplant the current vaccine.

First, the AS01B adjuvant is not currently licensed in the United States, so it is unclear if the HZ/su vaccine can get FDA approval.<sup>52,55</sup>

Second, there are several questions about the efficacy of the vaccine, including long-term efficacy, efficacy in the elderly, and efficacy in the case of a patient receiving only 1 of the 2 required doses.

Third, the impact of HZ/su vaccine on

complications such as postherpetic neuralgia has not been established. The clinical trial (NCT01165229) examining vaccine efficacy against postherpetic neuralgia incidence and other complications in adults age 70 and older has recently been completed and data should be available soon. Given the extremely high efficacy against HZ, it is likely that it will be close to 100% effective against this complication.

Fourth, there is uncertainty as to how the HZ/su vaccine should be used in patients who have already received the live-attenuated vaccine, if it is determined that a booster is necessary.

Finally, the vaccine is not yet priced. Given its superior effectiveness, particularly in older individuals, competitive pricing could dramatically affect the market. How Medicare or other insurers cover the new vaccine will likely influence its acceptance.

### ■ HZ VACCINATION OF IMMUNOCOMPROMISED PATIENTS

Immunocompromised patients are at highest risk for developing HZ. Unfortunately, there are currently no HZ vaccines approved for use in this population. The current live-attenuated vaccine has been demonstrated to be safe, well tolerated, and immunogenic in patients age 60 and older who are receiving chronic or maintenance low to moderate doses of corticosteroids.<sup>56</sup>

A clinical trial is being conducted to assess the immunogenicity, clinical effectiveness, and safety of the vaccine in rheumatoid arthritis patients receiving antitumor necrosis factor therapy (NCT01967316). Other trials are examining vaccine efficacy and safety in patients with solid organ tumors prior to chemotherapy (NCT02444936) and in patients who will be undergoing living donor kidney transplantation (NCT00940940). Researchers are also investigating the possibility of vaccinating allogeneic stem cell donors before donation in order to protect transplant recipients against HZ (NCT01573182).

### ZVHT and HZ/su vaccination in immunocompromised patients

Heat-treated varicella-zoster vaccine (ZVHT) is a potential alternative for immunocompro-

At older ages, the incidence of HZ and postherpetic neuralgia rises, making vaccination more cost-effective

mised patients. A 4-dose regimen has been proven to reduce the risk of HZ in patients receiving autologous hematopoietic-cell transplants for non-Hodgkin or Hodgkin lymphoma.<sup>57</sup>

In another trial, the 4-dose ZVHT was safe and elicited significant VZV-specific T-cell response through 28 days in immunosuppressed patients with solid tumor malignancy, hematologic malignancy, human immunodeficiency virus infection with CD4 counts of 200 cells/mm<sup>3</sup> or less, and autologous hematopoietic-cell transplants. The T-cell response was poor in allogeneic hematopoietic-cell transplant

recipients, however.<sup>58</sup>

Because the HZ/su vaccine does not contain live virus, it seems particularly promising for immunocompromised patients. In phase 1 and 2 studies, a 3-dose regimen has been shown to be safe and immunogenic in hematopoietic-cell transplant recipients and HIV-infected adults with CD4 count higher than 200 cells/mm<sup>3</sup>.<sup>59,60</sup> A phase 3 trial assessing the efficacy of HZ/su vaccine in autologous hematopoietic-cell transplant recipients is under way (NCT01610414). Changes in recommendations for HZ vaccine in these most vulnerable populations await the results of these studies. ■

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