

# **Vaccination for Prevention of Herpes Zoster**

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Herpes zoster is feared by many older patients and osteopathic physicians. Most of us can recall at least one patient that suffered greatly from herpes zoster. Morbidity from herpes zoster is significant and affects functionality as well as quality of life. The best prevention for the disease is through vaccination. This manuscript will review the background of the disease, discuss the current available vaccination, and explore the future of herpes zoster vaccination.

## **Herpes Zoster - Background**

Herpes zoster is a disease that most often presents later in life due to decline in cellular immunity with age and reactivation of the varicella zoster virus. After experiencing a primary infection with varicella zoster virus early in life, patients develop herpes zoster later in life due to reactivation of the varicella zoster virus from a latent infection of dorsal sensory or cranial nerve ganglia.<sup>1</sup> With a genome of approximately 70 gene products, varicella zoster virus is a double-stranded DNA herpesvirus.<sup>1</sup> All throughout life, varicella zoster virus attempts replication. However, cellular immunity declines with age and this allows the virus to reactivate and spread in the affected ganglia and sensory nerves to manifest on the skin.<sup>1</sup> The result is the painful rash diagnosed as herpes zoster.

The incidence of herpes zoster is high, especially among older patients. The incidence varies from 10 to 14 cases per 1000 annually in patients older than 65 years of age and it is estimated that the lifetime incidence is 20% to 30% in the general population.<sup>1-4</sup> However, the incidence greatly rises for patients 85 years of age and older. Incidence is estimated to be as high as 50% among patients age 85 and older.<sup>5</sup> Unfortunately, some patients suffer from recurrent infection after having recovered from the primary infection. It is estimated that there are approximately 1 million new cases of herpes zoster annually and recurrent herpes zoster is estimated to be 5.7% among immune-competent patients.<sup>6,7</sup> Recurrence is higher in immunocompromised patients.<sup>8</sup>

Strongest risk factors for herpes zoster include older age and suppression of cellular immunity.<sup>1</sup> Immunocompromised patients are at risk, including those with human immunodeficiency virus, Hodgkin's disease, non-Hodgkin's lymphoma, leukemia, bone marrow and organ transplants, systemic lupus erythematosus, rheumatoid arthritis, and patients taking immunosuppressive medications.<sup>1,5,6,8</sup> Additional risk factors include white race, female sex, and physical trauma.<sup>1,5,9,10</sup> The increase in incidence with age is most noted around ages 50 to 60 years and increases with age into late life in patients older than age 80 years.<sup>1-3</sup>

Some of the questions most commonly asked by patients about herpes zoster are pertaining to transmission. If a vesicular rash is present, patients may transmit herpes zoster through direct contact, airborne route, or droplet nuclei to other individuals.<sup>1,11</sup> Within 10 to 21 days after exposure, these individuals may subsequently have varicella.<sup>1</sup> However, if the rash has crusted or is only maculopapular, there is no risk of varicella zoster virus transmission.<sup>1</sup>

In addition to patients with immune disease, children who have not received the varicella vaccine, individuals with insufficient response to the vaccine, and vulnerable health professionals (especially those pregnant or immunocompromised) have increased risk for varicella from contact with patients with herpes zoster.<sup>1</sup> Unfortunately, vaccination for varicella in the pediatric population has not affected the incidence of herpes zoster in the United States.<sup>1,12</sup>

The best prevention of herpes zoster is through vaccination. At the time of writing of this manuscript, there is currently one approved vaccine available for prevention of herpes zoster-HZ (Zostavax® – Merck & Co, Inc) and another under investigation that is the herpes zoster subunit vaccine – HZ/su (Shingrix® – GlaxoSmithKline).



**Photos of Herpes Zoster**

Source: CDC, <https://www.cdc.gov/shingles/about/photos.html>, accessed 08/04/17

## **Herpes Zoster Vaccine (HZ Vaccine)**

In 2006, the live, attenuated HZ vaccine (Zostavax®) was approved by the United States Food and Drug Administration with an indication for prevention of herpes zoster in immunocompetent patients 60 years of age and older. Prior to this, the Shingles Prevention Study was conducted utilizing the vaccine. It is known that varicella zoster virus specific T cells decline with age and it is believed that the effectiveness of the vaccine is from restoration of varicella zoster virus specific T cells.<sup>14,15</sup> The Shingles Prevention Study was a randomized, placebo-controlled trial on 38,546 adults age 60 years or older. The HZ vaccine was compared to placebo and patients were followed for a mean of 3.12 years.<sup>14</sup> Endpoints of the study included burden of illness (incidence, severity, and duration) and incidence of postherpetic neuralgia. The HZ vaccine decreased the burden of illness from herpes zoster by 61.1% and the incidence of postherpetic neuralgia by 51.3%. Patients who were vaccinated and still developed herpes zoster were found to experience a milder form of the disease and duration was 3 days shorter for the vaccinated group as opposed to the placebo group.<sup>16</sup> Due to statistically significant results, the researchers determined that use of the HZ vaccine had greatly reduced morbidity from herpes zoster and occurrence of postherpetic neuralgia in older adults.<sup>14,17</sup> Based on the results of the Shingles Prevention Study, the HZ vaccine was approved by the United States Food and Drug Administration, Centers for Disease Control, and Prevention Advisory Committee on Immunization Practices (ACIP) for patients 60 years of age and older.<sup>16</sup> Since release of the vaccine, discussion has been around efficacy and cost effectiveness, uncertainty of the duration of the vaccine's protection, and possible need for a booster vaccination.<sup>14</sup>

### **HZ Vaccine Efficacy**

Efficacy was greater among the 60-69 year old patients than among the patients age 70 years and older in the Shingles Prevention Study.<sup>16</sup> However, additional studies of long-term efficacy have shown that initial vaccine efficacy is great but declines post-vaccine in years 3 to 11.<sup>18</sup> This has raised the question about need for booster vaccination as well as ignited studies for an additional vaccine. Despite the lack of long-term efficacy of the HZ vaccine, the vaccine has proven to decrease morbidity in patients by reducing the incidence of postherpetic neuralgia and decreasing the impact of herpes zoster on activities of daily living (ADL) and health-related quality of life (HRQL).<sup>18</sup> Additionally, studies have concluded that the vaccine is associated with reduction in incident herpes zoster.<sup>19</sup> Studies that have investigated effectiveness of the vaccine in patients with previous history of herpes zoster have found that patients age 50 years and older with a history of the disease tolerated the vaccine well and had an increase in the level of varicella zoster virus antibody over 4 weeks post-vaccination.<sup>20</sup> These study findings reinforce the recommendation of the ACIP for routine herpes zoster vaccination of all immunocompetent patients age 60 years of age and older including those with history of herpes zoster.<sup>20</sup>

## **HZ Vaccine Recommendations**

The tables below provide an overview of the CDC recommendations, FDA approval, and CDC contraindications/precautions for the HZ vaccine as of the date of writing of this manuscript. For complete and current information, the sources listed below should be accessed.

<b>Age/History</b>	<b>CDC Recommendation</b>	<b>FDA Approval</b>
60 years of age and older	Single dose vaccine	Yes
60 years of age and older with history of HZ	Single dose vaccine *no data exist regarding timing of vaccine after HZ episode, but general guideline for any vaccine is to wait until acute illness is over and symptoms subside*	Yes
50 to 59 years of age	No recommendation, risks/benefits of vaccination should be discussed with patient	Yes

Source: <https://www.cdc.gov/vaccines/vpd/shingles/hcp/hcp-vax-recs.html>, and <https://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm136941.htm>, accessed 07/18/17

## **HZ Vaccine Contraindications/Precautions from CDC**

Patients with Allergy	Life-threatening or severe allergic reaction to gelatin, neomycin, or other component of the vaccine.
Patients with Immune Disease/Immunodeficiency	HIV/AIDs or other diseases that affect the immune system, Cancer Treatment such as chemotherapy and radiation, Cancer Affecting Bone Marrow or Lymphatic System (such as leukemia and lymphoma), Patients taking immunosuppressive agents such as corticosteroids.
Pregnant Patients	Known pregnancy or patients who may be pregnant, patients should not become pregnant until at least 4 weeks after receiving vaccine (3 months per FDA).
Pediatric Patients	Vaccine is contraindicated. The vaccine is only approved for patients age 50 years and older (by the FDA).
Patients with Acute Illness	Patients with a minor acute illness (such as a cold) may be vaccinated. Patients with moderate to severe acute illness should wait until they recover to receive vaccine (this includes any patient with temperature of 101.3°F or higher).
Precaution on Transmission of Vaccine Virus	The FDA warns that the vaccine virus may be transmitted from vaccinee to susceptible contacts.

Sources: <https://www.cdc.gov/vaccines/vpd/shingles/hcp/hcp-vax-recs.html>, and <https://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm136941.htm>, accessed 07/18/17

## **HZ Vaccine Uptake**

Despite the known benefits of vaccination for prevention of disease, the HZ vaccine has experienced low uptake. The Healthy People 2020 target for HZ vaccine coverage in adults age 60 years and older is 30%.<sup>21</sup> Unfortunately, it is estimated that HZ vaccine coverage is 19.5% in adults age 60 years and older, thus below the Healthy People 2020 target.<sup>21</sup> Several studies have investigated causes for this low vaccine uptake. It has been found that patients more likely to receive the vaccine are female, immunocompetent, and visit the hospital, physician office, or pharmacy more often.<sup>21</sup> Additionally, patients receiving an influenza vaccine are also more likely to receive the HZ vaccine.<sup>21</sup>

Given the low percentage of patients receiving the immunization, there is great opportunity for osteopathic physicians to educate their patients on the HZ vaccine. However, it does not appear that we are maximizing our opportunities to provide this preventative care to our patients, or perhaps we have been faced with barriers that have prevented us from taking this action. According to one study, 90% of providers strongly recommended pneumococcal and influenza vaccinations to their patients, but only 41% strongly recommended HZ vaccination.<sup>22,23</sup> Why is this? It has been reported that several factors may have contributed to this slow vaccine uptake. Early on, there were shortages of the vaccine. There have also been cost barriers, as there has been great cost to providers to stock the vaccine. In addition to this, provider challenges with billing for the vaccine in the physician office have been an issue and the vaccine has been most available to patients when administered by pharmacists at a pharmacy.<sup>22</sup> As osteopathic physicians, our recommendations are of great importance to our patients. If a vaccine is not being recommended by a patient's physician or administered in the physician's office, many patients will not receive the vaccination. A systematic review of HZ vaccine acceptance found that the perspective of the study target group (patients age 50 years and older) was that the primary care physician's recommendation for vaccination was a crucial factor in achieving high vaccine uptake.<sup>23</sup> Knowledge is also a factor as some patients feel that their risk of herpes zoster is low and this has affected vaccine uptake.<sup>23</sup>

Finally, social determinants affect vaccine uptake. Studies have found correlation between social factors and vaccine uptake. Higher income, higher education, and not living alone have been associated with increased vaccine uptake.<sup>24</sup> Conversely, vaccine uptake is especially low in older patients living alone.<sup>24</sup> Understanding these factors that affect vaccine uptake will enable osteopathic physicians to target specific populations at most risk, educate these patients on the role of vaccines in prevention of disease, and assist patients with access.

## **Effects of Herpes Zoster on the Economy and Quality of Life**

Vaccination is key for prevention of disease. In addition to disease resulting in morbidity and mortality risk, disease also affects the economy and the patient's overall quality of life. Herpes zoster is no exception. Herpes zoster is known to have a negative effect on production at work for individuals with the disease and often results in absences as well as decrease in work effectiveness.<sup>25</sup> One study that looked at work time loss (defined as missing 1 partial or full work day or more) found that 57.7% of respondents in the study reported work time loss.<sup>25</sup> Health-related quality of life is also affected by the disease. Health-related quality of life (defined by five dimensions including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) is negatively affected by herpes zoster and specifically; patients with greater pain from the disease are more likely to have a lower health-related quality of life.<sup>25</sup>

Herpes zoster also carries an economic impact. For example, one study found that most commonly used resources by patients with herpes zoster include visits to the physician's office (79.1% of patients), visits to the emergency room (48.8% of patients), specialist visits (37.9% of patients), and hospitalization (5.7% of patients).<sup>26</sup> It is estimated that the cost per episode of herpes zoster is \$1,464.59.<sup>26</sup> Costs are higher in patients with postherpetic neuralgia and are estimated to be \$2,001.13 per case.<sup>26</sup> The costs and effects on quality of life associated with herpes zoster warrant strong measures to provide effective and affordable vaccination as a means to prevention of the disease.

## **Herpes Zoster and Additional Risk - Stroke and Myocardial Infarction**

At the time of writing of this manuscript, there have been recent publications bringing attention to herpes zoster increasing the risk of stroke and myocardial infarction. Previously, it was published that there is indication that patients with herpes zoster infection are at risk for ischemic stroke in the short term period after the acute infection (within 3 months).<sup>27</sup> However, there was not a significant association found with risk for hemorrhagic stroke.<sup>27</sup> Most recently, a published study found that risk of stroke was highest in younger patients (under 40 years of age) after herpes zoster infection and the risks of stroke and myocardial infarction were highest within one year after acute herpes zoster infection and then decreased.<sup>28</sup> Furthermore, the study found that herpes zoster increased the risks of cardiovascular events by 41%, stroke by 35%, and myocardial infection by 59% in patients 40 years of age and older.<sup>28</sup> These significant risks are additional evidence that prevention of this disease is paramount.

## **The Future in Vaccination for Prevention of Herpes Zoster**

Given the morbidity often associated with herpes zoster as well as influence on decrease in quality of life, increase in cost, and long-term health risks after the acute illness, it is essential that efficacy of vaccination against herpes zoster be improved. Based on research, it has been shown that a booster dose of the current live, attenuated vaccine (Zostavax®) increases immunity against herpes zoster when given ten years after the first vaccination to patients older than age 70 years.<sup>29,30</sup> This has brought the concept of booster vaccination against herpes zoster into question and at the time of writing of this manuscript, there is also an additional herpes zoster vaccine (Shingrix®) under investigation.

Shingrix® (GlaxoSmithKline) is an investigational, non-live, herpes zoster vaccine that is known as HZ/su as it is a subunit vaccine that expresses immunogenic varicella zoster virus proteins.<sup>29</sup> The vaccine uses adjuvanted recombinant varicella zoster virus glycoprotein E (ORF68) and has been investigated using two doses of the vaccine (another dose given two months after the first dose).<sup>29,31</sup> As physicians await decisions regarding the investigation and official recommendations, it has been noted that subunit vaccines like HZ/su are often determined to be safe for patients that are not able to receive live attenuated vaccines and are known to produce a strong immune response.<sup>29</sup>

In September 2016, the *New England Journal of Medicine* published results of a randomized, placebo-controlled, phase 3 trial investigating the HZ/su vaccine.<sup>32</sup> The trial was conducted in 18 countries. Study participants were age 70 years and older and received two doses of HZ/su with the second dose administered two months after the first. The study investigated efficacy of the vaccine against herpes zoster and postherpetic neuralgia. Prior to this study, another phase 3 trial investigated efficacy of the HZ/su vaccine in patients age 50 years and older.<sup>32</sup> This study found that the HZ/su vaccine was associated with 97.2% lower risk of herpes zoster than placebo.<sup>32</sup> In the most recent trial involving participants age 70 years and older, vaccine efficacy against herpes zoster was 89.8% and vaccine efficacy against postherpetic neuralgia was 88.8%.<sup>32</sup> There was no distinct difference between efficacy in participants ages 70 to 79 years and those 80 years of age and older. Efficacy in the 70 to 79 years age group was found to be 90.0% and efficacy in the group age 80 and older was found to be 89.1%.<sup>32</sup> The mean follow up- period was 3.7 years.<sup>31</sup>

Most recent investigation of the HZ/su vaccine has involved participants age 50 years and older who previously received the live, attenuated HZ vaccine a minimum of 5 years prior to receiving the HZ/su vaccine.<sup>33</sup> In late June 2017, it was reported that this study concluded that participants produced a strong immune response to the HZ/su vaccine.<sup>34</sup> At the time of writing of this manuscript, the HZ/su vaccine is under FDA review and the CDC has not made a recommendation regarding the vaccine. The most recent investigation results were presented to the Advisory Committee on Immunization Practices (ACIP) at their June 21, 2017 meeting. It is

expected that an official vote on recommendations for the HZ/su vaccine will occur in Fall 2017.

In closing, there are several factors that will likely be considered prior to official decisions being made on recommendations for the HZ/su vaccine. Many of these factors will affect decision on recommendation and others will affect vaccine uptake. Possible barriers to vaccine uptake include the compliance risk with use of a two dose schedule as opposed to a single dose, unknowns about vaccine coverage and cost, and adverse reactions as there has been a high rate of common adverse reactions to the vaccine observed during investigation.<sup>31</sup> For now, osteopathic physicians will await information from the FDA review of the HZ/su vaccine and anticipate additional information from the ACIP in Fall 2017.

### **Addendum to Manuscript – November 7, 2017**

Since the date of the above original manuscript (July 20, 2017), there have been further developments in the review of the HZ/su vaccine. On October 20, 2017; the FDA approved the HZ/su (Shingrix®) vaccine and the ACIP voted on October 25, 2017 to recommend the vaccine for immunocompetent adults age 50 years and older and to revaccinate individuals that have previously received the HZ (Zostavax®) vaccine.<sup>35,36</sup> It should be noted that this age recommendation differs from the current shingles vaccination guideline to vaccinate those age 60 years and older. The CDC will review the ACIP recommendations and a decision will be made by the CDC about final approval and official CDC vaccine recommendations.<sup>35</sup> The ACIP recommendations are not official CDC vaccine recommendations until reviewed and approved by the CDC as well as published as official CDC vaccine recommendations.

Furthermore, the ACIP voted in favor for the HZ/su (Shingrix®) vaccine to be preferred over HZ (Zostavax®) vaccine for the prevention of herpes zoster and complications.<sup>35</sup> This was a very close vote with eight committee members voting in favor and seven opposed.<sup>35</sup> According to Committee Chair, Nancy Bennett M.D., this was the closest vote she has witnessed during her time serving on the committee.<sup>35</sup> According to reports, there was caution expressed within the committee about preferential recommendation being given for a new vaccine and there was also concern about vaccine supply.<sup>35</sup> Additionally, there was concern voiced about the vaccine containing a new adjuvant that is known to increase the immune response of the vaccine.<sup>36</sup> Information is still being collected to investigate the vaccine's efficacy and safety in immunocompromised individuals.<sup>36</sup> Although the vaccine has demonstrated positive efficacy, it has been associated with more adverse reactions and this has also raised some caution and likely contributed to the close vote.<sup>37</sup>

Official CDC review, approval, and recommendations for the HZ/su (Shingrix®) vaccine are pending at this time. The vaccine is expected to be on the market in the United States by late November 2017.<sup>36</sup> However, it is expected that it will be 2018 before agreements will be made with insurances for reimbursement for the cost of the vaccine.<sup>36</sup> The current reported cost for Shingrix® (given in two doses) is \$280



total per patient and the reported cost of Zostavax® (given in one dose) is \$223 total per patient.<sup>36</sup>

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