



### August 2008: VOLUME 1, NUMBER 9

#### *Herpes Zoster and Varicella Zoster Vaccine*



#### In this Issue...

Herpes Zoster (HZ), caused by reactivation of latent varicella zoster virus (VZV) in the dorsal root ganglion, can cause acute as well as chronic morbidity through painful cutaneous eruptions as well as chronic postherpetic neuralgia. Immunocompromised patients and older patients are at increased risk for HZ. The use of a live attenuated vaccine for the prevention of HZ and its sequelae in immunocompetent adults 60 years and older was approved by the U.S. Food and Drug Administration on May 25, 2006.

In this issue, we review the recent recommendations the Advisory Committee on Immunization Practices (ACIP) has made in the CDC Morbidity and Mortality Weekly Report on the prevention of HZ with the use of the herpes zoster vaccine, as well as the Shingles Prevention Study which led to many of these recommendations. We will also review the treatment of localized herpes zoster in immunocompromised patients, and further risk factors for herpes zoster.

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#### Length of Activity

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#### Release Date

August 12, 2008

#### Expiration Date

August 11, 2010

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Professor of Pediatrics and Dermatology and Director of Pediatric Dermatology, Johns Hopkins Children's Center  
Baltimore, MD

##### **Susan Matra Rabizadeh, MD, MBA**

Private Practice  
Los Angeles, CA

##### **Mark Lebwohl, MD**

Professor and Chairman  
Department of Dermatology  
The Mount Sinai School of Medicine  
New York, NY

##### **Elizabeth Sloand, PhD, CRNP**

Assistant Professor of Pediatric Nursing  
The Johns Hopkins University  
School of Nursing  
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## GUEST AUTHORS OF THE MONTH



Commentary & Reviews:  
**Parisa Ravanfar, MD,  
MBA, MSc**  
Clinical Research Fellow  
Center for Clinical Studies  
Houston, Texas



Commentary & Reviews:  
**Brenda Bartlett, MD**  
Clinical Research Fellow  
Center for Clinical Studies  
Houston, Texas



Commentary & Reviews:  
**Stephen K. Tying, MD,  
PhD, MBA**  
Clinical Professor  
The University of Texas  
Medical School  
Houston, Texas

### **Guest Faculty Disclosures**

**Dr. Ravanfar** has indicated no relationships with commercial supporters.

**Dr. Bartlett** has indicated no relationships with commercial supporters.

**Dr. Tying** has disclosed that he has received grants for clinical research and educational activities from, has served as an advisor, consultant and speaker to, and/or has served as an investigator for Abbott, Amgen, Catalyst, Epiphany, Galderma, Genentech, GSK, Merck and Novartis.

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## LEARNING OBJECTIVES

**At the conclusion of this activity, participants should be able to:**

- Describe to colleagues the safety and efficacy of the herpes zoster (HZ) vaccine
- Know to which patients the herpes zoster vaccine should be recommended to and know for which patients it is contraindicated according to the current CDC report
- Discuss with colleagues the management of non-disseminated herpes zoster in immunocompromised patients

## COMMENTARY

An estimated 1 million cases of HZ occur annually in the United States. A remarkable 25% of patients with a history of chickenpox will develop HZ later in life.<sup>1</sup> HZ can significantly affect quality of life, not only acutely from the painful lesions, but also chronically due to postherpetic neuralgia (PHN) as well as due to ocular involvement leading to potential vision loss. The incidence of HZ increases with age, as does the prevalence of PHN. With the introduction of the zoster vaccine, the morbidity from HZ can be significantly reduced. In a large multicenter study (The Shingles Prevention Study), Oxman et al. evaluated the efficacy and safety of the zoster vaccine. The study was a randomized, double-blinded, placebo-controlled trial of the live attenuated Oka/Merck zoster vaccine with 38,546 adults age 60 or older. The clinical trial provided evidence that vaccination against VZV decreases the incidence and severity of both HZ and PHN among older adults. The vaccine was also evaluated for safety and the only significant reactions found were non-serious adverse reactions; primarily mild reactions at the injection site. Statistically significant reactions included erythema, pain or tenderness, swelling, and pruritus at the injection site. There were also reports of a rare varicella-like rash at the injection site.

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Serious adverse reactions were few and not statistically significant. Overall, the vaccine appears to be very safe relative to other live-attenuated vaccines on the market.

All dermatologists should familiarize themselves with the key recommendations of the CDC on administration of the zoster vaccine, as both their colleagues and their patients will be requesting information on the vaccine.

Unfortunately, the zoster vaccine is contraindicated in immunocompromised patients who are at significantly higher risk of HZ. The incidence of HZ is at least two times greater in immunocompromised patients and cases are more severe compared to those seen in immunocompetent patients.<sup>2</sup> Disseminated VZV is likewise more common in immunocompromised patients. Therefore, safe and effective treatment for HZ is still a pertinent and extremely significant issue.

Immunocompromised patients with disseminated HZ must be hospitalized and given IV acyclovir. In non-disseminated HZ, Arora et al. demonstrated that valacyclovir given 1 gram TID is just as effective in treating the immunocompromised patient as compared to 2 grams TID. Further studies need to be performed on treatment of HZ in immunocompromised patients.

Identifying those at risk for HZ, such as the elderly, and the immunocompromised can further assist the clinician in evaluating a patient for zoster vaccine administration. Interestingly, a recent publication by Hicks et al. demonstrated a positive family history of shingles, especially in those with multiple relatives with HZ, may also be a risk factor.

Many dermatologists strongly encourage the administration of the zoster vaccine as a routine practice.<sup>3</sup> Further vaccine studies are currently being conducted in younger individuals and in the mildly immunocompromised. Currently, the zoster vaccine should be administered to all eligible patients 60 years or older and dermatologists should offer the vaccine to all patients that qualify.

## References

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2. Gourishankar S, McDermid JC, Jhangri GS, Preiksaitis JK. [Herpes zoster infection following solid organ transplantation: incidence, risk factors and outcomes in the current immunosuppressive era](#). *Am J Transplant*. 2004;4:108-115.
3. A.Y. Zhang, C.A. Elmets, W.L. Camp and B.W. Elewski. [New opportunities in preventive dermatology: how far should we go?](#) *J Am Acad Dermatol*. 2007;56(4):675-676.

## SAFETY AND EFFICACY OF THE HERPES ZOSTER VACCINE

Oxman MN, Levin MJ, Johnson GR, et al. **A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults**. *N Engl J Med*. 2005;352:2271-2284.

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The objective of this study was to test the hypothesis that vaccination against varicella-zoster virus (VZV) would decrease the incidence, severity, or both of herpes zoster (HZ) and postherpetic neuralgia (PHN) among older adults. This study was a randomized, placebo-controlled, double-blinded clinical trial conducted at 22 sites, in which subjects 60 years of age or older received either a single subcutaneous 0.5-mL injection of an investigational live, attenuated Oka/Merck VZV vaccine or placebo. Eligible patients had a history of varicella or had resided in the continental US for at least 30 years. The study excluded immunocompromised patients and those with a history of shingles. The primary end-point was the burden of illness due to HZ. The secondary outcome in this study was the incidence of PHN, defined as pain associated with HZ rated as at least a 3 on a pain scale of 0-10, persisting or appearing more than 90 days after the onset of the lesion.

The study enrolled a total of 38,546 subjects. There were 1308 suspected cases of HZ, 1156 of which the final diagnoses were based on PCR assay results. Of the 1308 cases of

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suspected HZ, 984 (75.2%) were confirmed cases of HZ. The use of antiviral medication for HZ was similar in both groups. The burden-of-illness score due to HZ was significantly reduced in the vaccine arm as compared with the placebo arm (2.21 vs 5.86;  $p < 0.001$ ). The vaccine efficacy with respect to burden-of-illness was 61.1% (95% CI, 51.1-69.1). There were 107 cases of PHN, 27 in the vaccine arm and 80 in the placebo arm. Thus, the vaccine was efficacious in the reduction in the incidence of PHN (66.5%, 95% CI, 47.5 - 79.2). A significant reduction in the overall incidence of HZ per 1000 person-years by the zoster vaccine (11.12 per 1000 person-years in the placebo group, vs. 5.42 per 1000 person-years in the vaccine group;  $p < 0.001$ ) was observed. Efficacy of the vaccine with respect to the incidence of herpes zoster was 51.3% (95% CI, 44.2-57.6). The vaccine was more efficacious in preventing herpes zoster in subjects aged 60-69 compared to subjects 70 years of age and older (63.9% vs. 37.6%;  $p < 0.001$ ). The median duration of pain and discomfort due to zoster was found to be shorter than in the vaccine group than in the placebo group (21 days vs. 24 days,  $p = 0.03$ ). The mean severity-of-illness score in subjects with HZ was also significantly lower in the vaccine group compared to the placebo group (141.2 vs 180.5,  $p = 0.008$ ). Furthermore, the effect of the vaccine on the severity of illness was greater among the older subjects. The vaccine efficacy with respect to the burden of illness due to HZ was 55.4%.

With respect to safety of the vaccine, during the first 42 days after vaccination, the number and types of serious adverse events in the vaccine group were analogous to those experienced in the placebo group. A significant non-serious adverse event in the vaccine group compared to placebo was a varicella-like rash at the injection site (0.1% vs. 0.04%). The study also went on to perform an adverse events substudy, which found that patients in the vaccine group had a significantly greater amount of adverse events at the injection site which, in order of occurrence, consisted of erythema, pain or tenderness, swelling, and pruritus. The percentage of subjects with  $\geq 1$  serious adverse event was comparable in both groups; however, those adverse events considered vaccine-related were more common in the vaccinated group.

Based on this significant data, the zoster vaccine was found to greatly decrease the morbidity associated with herpes zoster and the incidence of postherpetic neuralgia. The investigators not only demonstrated the vaccine to be successful through all primary and secondary outcome measures, but proved it to be a relatively safe vaccine as well.

## CDC RECOMMENDATIONS AND CONTRAINDICATIONS FOR THE HERPES ZOSTER VACCINE

Harpaz R, Ortega-Sanchez IR, Seward JF; Advisory Committee on Immunization Practices (ACIP) Centers for Disease Control and Prevention (CDC). **Prevention of herpes zoster: recommendations of the Advisory Committee on Immunization Practices (ACIP).** *MMWR Recomm Rep.* 2008 Jun 6;57(RR-5):1-30; quiz CE2-4. Erratum in: *MMWR Recomm Rep.* 2008 Jul 18;57(28):779.

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The zoster vaccine that is licensed for use in the US, uses the Oka/Merck strain of live attenuated VZV that is the same strain used in the varicella vaccine. ACIP states that the zoster vaccine should be administered as a one-time, subcutaneous, 0.65mL dose in the deltoid region. The vaccine is not approved as a booster dose. The main points of attention will be reviewed here.

The ACIP recommends vaccination with one dose of the zoster vaccine to persons 60 years or older. Those with a previous history of zoster and those with a chronic medical disease, unless otherwise contraindicated, are candidates for receiving the zoster vaccine. Obtaining patients' past medical history of varicella or serologic testing are unnecessary. The zoster vaccine can be administered with other vaccines during the same visit, but with different syringes and at different anatomic sites. If such vaccines cannot be given at the same visit, then the CDC recommends waiting at least 4 weeks before or after another live attenuated vaccine, but the zoster vaccine can be administered any time before or after an inactivated vaccine. The zoster vaccine is not licensed for persons less than 60 years of age. Those with a history of zoster can still be vaccinated, although there is currently no data supporting that it prevents recurrence. Patients over 60 years old who anticipate initiating immunosuppressive treatment, or whose disease state may lead to immunodeficiency, are recommended to receive 1 dose of the zoster vaccine at the first

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possible clinic visit while their immunity is still intact. The ACIP recommends that the zoster vaccine be administered at least 14 days before the start of immunosuppressive therapy; however 1 month prior would be ideal, if possible.

In the case of patients taking antiviral medications, such as acyclovir, famciclovir, and valacyclovir, these medications should be discontinued if possible at least 14 days prior to the administration of the zoster vaccine and should not be used at least 14 days after vaccination. The zoster vaccine can also be administered at anytime before, after, or during the transfusion of blood or any other antibody-containing blood product. Varicella vaccine, like most other live vaccines, is not secreted in breast milk and breastfeeding is therefore not contraindicated for zoster vaccination, although this would be very uncommon in the age group for which this vaccine is licensed.

Contraindications to the vaccine include:

- A history of an anaphylactic reaction to any component of the vaccine, including gelatin and neomycin. Of note, neomycin allergy in the form of contact dermatitis is not a contraindication.
- Primary or acquired immunodeficiency, with the following specifications:
  1. Persons with leukemia, lymphoma, or malignancy affecting the bone marrow or lymphatic system are contraindicated; however, patients who are in remission from leukemia and who have not received chemotherapy or radiation for at least 3 months are not contraindicated from receiving the vaccine .
  2. Persons with AIDS or clinical manifestations of HIV, including those with CD4+ count < 200/mm<sup>3</sup> or <15% of total lymphocytes.
  3. Persons on immunosuppressive therapy, including high dose corticosteroids. The ACIP recommends administering the vaccine at least 1 month after discontinuation of immunosuppressants. Of particular significance to dermatologists is that short-term (<14 days) corticosteroids, low-to-moderate dose, topical, intra-articular injections, or long-term alternate day treatments with short-acting steroids, are not contraindications to the vaccine. According the ACIP, low-doses of methotrexate, azathioprine, or 6-mercaptopurine for treatment of conditions such as psoriasis, dermatomyositis, inflammatory bowel disease, sarcoidosis or rheumatoid arthritis are also not absolute contraindications to administration of the vaccine; however, the Medical Board of the National Psoriasis Foundation (Lebwohl et al.) states that live vaccine administration should be avoided in those on biologics.
  4. Persons with impaired humoral immunity can receive the zoster vaccine, but those with clinical or laboratory evidence of cellular immunodeficiency can not.
  5. Persons undergoing hematopoietic cell transplant should be carefully evaluated by the physician and determined on a case-by-case basis. If vaccination is determined to be appropriate, administration is recommended at least 24 months after transplant.

Due to the unknown safety and efficacy of zoster vaccine with concurrent use of recombinant immune mediators and immune modulators, such as the tumor necrosis factor inhibitors, adalimumab, infliximab, and etanercept, physicians should evaluate the immune status of each patient on a case-by-case basis to assess the risks and benefits. According to Lebwohl et al. live vaccines should be avoided in patients on such therapies. If the clinician assesses the patient and decides to administer the vaccine, the ACIP recommends that the vaccine be given at least 1 month after discontinuation of these agents. The vaccine can also be administered to patients with acute illness, but should be postponed in patients with severe acute illness or those with fevers of 100.4F or greater until after recovery.

## References

1. Lebwohl M, Bagel J, Gelfand JM, Gladman D, Gordon KB, Hsu S, Kalb RE, Kimball AB, Korman NJ, Krueger GG, Mease P, Morison WL, Paller A, Pariser DM, Ritchlin C, Strober B, Van Voorhees A, Weinstein GD, Young M, Horn L. [From the Medical Board of the National Psoriasis Foundation: monitoring and vaccinations in patients treated with biologics for psoriasis.](#) *J Am Acad Dermatol.* 2008 Jan;58(1):94-105. Epub 2007 Nov.

## IMMUNE RESPONSE IN THE ELDERLY TO THE ZOSTER VACCINE

Levin MJ, Oxman MN, Zhang JH, et al. Veterans Affairs Cooperative Studies Program Shingles Prevention Study Investigators. **Varicella-zoster virus-specific immune responses in elderly recipients of a herpes zoster vaccine.** *J Infect Dis.* 2008;197(6):825-835.

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This is an immunologic substudy of the above described “Shingles Prevention Study”. The objective of this study was to demonstrate the relationship between the measured VZV-specific immune responses to the zoster vaccine in the study and clinical outcome, in particular, the occurrence of herpes zoster.

This was a double-blind, placebo-controlled trial that enrolled consented subjects from two study sites concurrently into the shingles prevention study and the immunology substudy, N=1395 for this substudy. The substudy subjects were tested for VZV-CMI (VZV-specific-T-cell mediated immunity) and antibodies to VZV glycoproteins at baseline (before vaccination), 6 weeks post-vaccination, and yearly for the next 3 years. VZV-CMI was measured by a responder cell frequency assay (RCF) and also measured by an ELISPOT assay. VZV-specific antibodies were measured by use of a quantitative ELISA method (gpELISA) that detected antibodies to VZV glycoproteins purified from VZV-infected human fibroblasts.

A regression analysis of VZV-CMI responses at baseline demonstrated an expected decrease in immune response with increase in age ( $p < 0.001$ ). Although the baseline VZV-specific RCF and ELISPOT levels were lower in the older age group ( $> 70$  years), age was found to have no significant effect on the VZV antibody (gpELISA titers,  $p = 0.75$ ). The authors examined the effect of age on VZV-specific immunity as measured by all three assays. The estimated annual decrease in the level of VZV-CMI per year of increase in age was 2.7% for RCF ( $p < 0.001$ ) and 3.9% for ELISPOT ( $p < 0.001$ ). The age-related decline in gpELISA levels was insignificant. The VZV-CMI responses at 6 weeks after vaccination declined with age and were significantly lower in patients 70 years of age and older compared to patients 60-69 years of age ( $p < 0.001$  for RCF,  $p < 0.001$  for ELISPOT). The authors observed a decline of 3.5% and 3.8% in RCF and ELISPOT responses, respectively, per age-year at week 6. After the correction for age, sex, and study site, the levels of VZV-specific immunity achieved after vaccination strongly correlated with the degree of the corresponding baseline levels for all 3 assays ( $p < 0.001$ ). Another measured outcome was the immune responses in patients who developed HZ compared to patients who did not develop HZ. Analyses revealed a significant inverse relationship between the 6 week immune responses after vaccination and the risk of HZ. Furthermore, the authors demonstrated lower VZV-specific responses in patients who developed HZ ( $P < 0.001$  to  $p < 0.03$  for 3 assays). Although the authors were successful in demonstrating that the magnitude of the CMI response to VZV was inversely correlated with the likelihood of developing HZ, they were unable to identify a surrogate marker or threshold level of protection.

This study provided evidence that humoral immune responses are not protective against HZ. Instead, VZV-specific T-cell mediated immunity paralleled the clinical outcomes of the vaccine observed in the efficacy study. This substudy also provides an explanation of the finding in the main study by Oxman et al. that the vaccine was more efficacious in preventing herpes zoster in subjects aged 60-69 compared to subjects 70 years of age and older since the VZV-CMI was found to be lower in the older age group.

## TREATMENT OF HERPES ZOSTER IN IMMUNOCOMPROMISED PATIENTS

Arora A, Mendoza N, Brantley J, Yates B, Dix L, Tying SK. **Double-Blind Study Comparing 2 Dosages of Valacyclovir Hydrochloride for the Treatment of Uncomplicated Herpes Zoster in Immunocompromised Patients 18 Years of Age and Older.** *J Infect Dis.* 2008;197(9):1289-1295.

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The objective of this study was to assess the safety and efficacy of an oral dosage of valacyclovir, 1gram TID vs 2 grams TID for the treatment of herpes zoster in immunocompromised adult patients. This study was a randomized, double-blind, controlled clinical trial. Eligible patients had to have immune dysfunction due to congenital immune deficiency, active internal malignancy, collagen vascular disease, organ or bone marrow transplantation, known infection with HIV, and/or known to have received cytotoxic drugs or immunosuppressive therapy in the past 3 months. Exclusion criteria included: evidence of cutaneous or visceral dissemination of HZ, receipt of topical or systemic anti-VZV medications in the previous 4 weeks, abnormal liver function tests (LFT), impaired renal function, or a history of intolerance or hypersensitivity to anti-viral medications.

The primary endpoint was the time to full resolution of zoster-associated pain (ZAP). The secondary outcome measurements were the time to cessation of zoster-associated abnormal sensation (ZAAS), percentage of days 1-28 with ZAP and/or ZAAS, percentage of weeks 1-24 with ZAP and/or ZAAS, days to complete healing of zoster-associated rash, and percentage of patients with zoster-associated complications. The study enrolled 87 patients (45 of whom received 1g TID and 42 of whom received 2 g TID) of which 63 completed the study. Both treatment groups had similar demographics and clinical characteristics without any statistically significant differences. The majority of patients had solid organ cancer and were undergoing chemotherapy and/or radiation. The authors conducted a multivariate analysis of the time to cessation of ZAP. The only covariate in the multivariate model that was found to be statistically significant was baseline rash severity ( $p=0.03$ ). Patients who had a mild rash had a shorter duration of zoster-associated pain as compared to patients with moderate or severe rashes (hazard risk=0.44). Analysis of the time to cessation of zoster-associated abnormal sensation was similar in both treatment groups, with no statistically significant difference. There was no significant difference between treatment groups in the duration from initiation of treatment to full crusting; with median times of healing at 8 days in both groups.

Based on the study results that demonstrated analogous healing time between valacyclovir 1g TID and valacyclovir 2 g TID, the authors conclude that the lower dosage treatment would be more cost-effective without compromising treatment efficacy. The authors recommend further studies with these patients to confirm these findings. Since immunocompromised patients are at significantly increased risk of HZ infection, but are contraindicated from receiving the zoster vaccine, this study is of benefit in the treatment of zoster in immunocompromised patients. It should be noted that the study also excluded severely immunocompromised patients, such as HIV+ patients with CD4 counts  $<50$  cells/mm<sup>3</sup> and bone marrow, liver, or heart transplant patients within 9 months after transplantation.

## NEW RISK FACTORS FOR HERPES ZOSTER

Hicks LD, Cook-Norris RH, Mendoza N, Madkan V, Arora A, Tying SK. **Family History as a Risk Factor for Herpes Zoster: A Case-Control Study.** *Arch Dermatol.* 2008;144(5):603-608.

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The objective of this case-controlled study was to determine if there is an increased risk factor for HZ in patients with a family history of HZ. Subjects were adults with confirmed HZ that were examined and treated between January 1, 1992 and August 15, 2005 at the Center for Clinical Studies in Houston, Texas. Cases of HZ were diagnosed by a staff dermatologist. So as to diminish bias, controls were chosen among current patients and past immunocompetent patients from the same center as the case patients. The selected control subjects were age, sex, and race matched by investigators different from those conducting the blinded standardized questionnaire and those controls found to be immunocompromised were excluded. Two medically-trained, blinded investigators conducted the standardized interview and both cases and controls were asked a series of questions, which included demographic data, and HZ history in blood relatives. All controls who answered yes to any of the questions connected to having a positive HZ history were excluded from the study. Previous HZ vaccination was not a confounding factor in this

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study, as the vaccine was not yet approved by the FDA during the investigation portion of this study.

The primary study variable was a history of HZ. From a database of 1114 eligible patients, 504 well-documented cases of HZ and 523 controls were enrolled in the final study. Family history obtained on immunocompromised blood relatives was excluded in both case and control groups. The authors analyzed the distribution of cases and controls according to family history of HZ. A significantly higher percentage of cases reported a family history of HZ as compared to controls (39.9% vs. 10.5%;  $p < 0.001$ ). Cases were 4.35 times more likely than controls to have a first degree relative with HZ (95% CI, 3.11-6.09) as well as 4.27 times more likely to have non-first degree relatives with HZ than controls (95% CI, 2.44-7.49). The OR for total affected relatives was 4.09 (95% CI, 3.06-5.47). Furthermore, the authors calculated an OR of 4.50 (95% CI, 3.15-6.41) for those that reported one relative with history of HZ, and an OR 13.77 (95% CI, 5.85-32.39) for those that reported a history of multiple relative with HZ; therefore suggesting a dose-dependent effect. The authors also executed a logistic regression model in which sex, age, race, and total number of relatives were all used as variables for the prediction of HZ. Interestingly, the only variable that the authors found to be a statistically significant predictor of HZ when all other variables were held constant was the total number of relatives with history of HZ.

Limitations of this study include possible recall bias in the association between HZ and family history of HZ. Further studies are needed to confirm these results, ideally in the form of prospective cohorts. Nevertheless, this study provides useful data in predicting those at risk for HZ, beyond the patient's age and immune status. This information can be of benefit to clinicians when evaluating a patient for the receipt of the zoster vaccine.

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## Learning Objectives — [back to top](#)

At the conclusion of this activity, participants should be able to:

- Describe to colleagues the safety and efficacy of the herpes zoster (HZ) vaccine
- Know to which patients the herpes zoster vaccine should be recommended to and know for which patients it is contraindicated according to the current CDC report
- Discuss with colleagues the management of non-disseminated herpes zoster in immunocompromised patients

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