When Hope-Simpson identified the role of declining varicella-zoster virus (VZV) immunity in the pathogenesis of herpes zoster in the 1960s, he opened the door to a surge of research into both the evolving patterns of cell-mediated immunity (CMI) in aging and immunocompromised individuals and the impact of these changes in immunity on the development of shingles in adults. These investigations helped to document the hematologic persistence of VZV antibodies over time, the evidence of a reduction in CMI to VZV that occurs with advancing age, and the role of this declining immunity in the development and severity of herpes zoster disease. It also became clear that repeated exposure to VZV can reverse this decline in CMI in immunocompetent adults, thereby potentially averting the reactivation of latent VZV that is responsible for the occurrence of herpes zoster disease.

Prevention of herpes zoster in older adults has been recognized as a medical priority for many reasons. Although the incidence of zoster is relatively low in young people, the incidence of zoster increases dramatically after age 50 years. As many as 50% of individuals who live to age 85 years will have herpes zoster at some point in their lives. Zoster disease carries the risk of long-term complications, including postherpetic neuralgia (PHN), a common debilitating sequela of herpes zoster that affects 65% of patients aged 60 years or older.

The antiviral and corticosteroid drugs traditionally used to treat patients for acute herpes zoster episodes provide limited efficacy in preventing these problems. Consequently, many patients suffer the distressing complications and the negative impact on quality of life that these sequelae are known to cause. Thus, research has focused on disease prevention, predominantly via immunization with a booster vaccine able to increase CMI to VZV to protect against the onset of herpes zoster disease.

The US Food and Drug Administration’s recent approval of a live attenuated vaccine to prevent herpes zoster in individuals aged 60 years or older has the potential to greatly reduce the burden of herpes zoster and its complications, including PHN, in this age group. This indication was based primarily on data from the Shingles Prevention Study (SPS), the design and outcomes of which are reviewed in this article.

The Shingles Prevention Study
Recognition of the impact of herpes zoster on adults led to the development of a much more potent formulation of the currently available childhood chickenpox (varicella) vaccine. The zoster vaccine, targeted for adults, is a live attenuated vaccine containing the same virus strain as the varicella vaccine for children, but modified to 14 times the potency. The SPS established the efficacy and safety of the zoster vaccine.
and provided the data that formed the basis for the US Food and Drug Administration’s approval of the vaccine for the prevention of herpes zoster in adults aged 60 years or older.

**Study Design**

The SPS was a randomized double-blind placebo-controlled trial designed to evaluate the efficacy and safety of the zoster vaccine in preventing the occurrence of herpes zoster, as well as its most common complication, PHN. The study was conducted at 22 study sites across the United States and enrolled 38,546 adults aged 60 years or older with no prior cases of herpes zoster, but with a history of varicella or who resided in the United States for at least 30 years. Those with a prior history of zoster were excluded from the study. Of this population, 46% were at least 70 years old and more than 6.5% were aged 80 years or older. Immuno-compromised individuals and those unable to adhere to the study protocol were excluded from entry.

Subjects were randomly assigned to receive a single subcutaneous injection of either 0.5 mL of the zoster vaccine or placebo. Study participants were asked to contact their study site in the event of rash or unilateral pain. Surveillance was further ensured by a well-defined interactive and automated telephone-response system, which participants called monthly. Study subjects who were suspected to have herpes zoster or who failed to call their study site, were contacted for follow-up. The diagnosis of herpes zoster was based on established clinical and laboratory features, and associated pain and discomfort were assessed repeatedly for at least 6 months after diagnosis. Follow-up was maintained for a mean of 3.13 years (maximum 4.90 years).

The primary end point of the study was the burden of illness (BOI) due to herpes zoster. This end point was defined as a composite measure of incidence, severity, and duration of zoster-related pain and discomfort. Pain was assessed using the Zoster Brief Pain Inventory, a questionnaire that patients answered after the onset of herpes zoster to measure their zoster-associated pain and discomfort. The numerical value of the patients’ BOI was plotted over time, and a score was derived from the area under the curve of these values. The secondary end point was the incidence of PHN, determined by pain persisting beyond 90 days from onset of the zoster rash. An additional finding was the incidence of herpes zoster, though this was not an initial end point in the study.

**Results**

**Patient Population**

A total of 38,546 subjects aged 60 years or older were enrolled in the study; 19,270 subjects were assigned to receive the active zoster vaccine (study group) and 19,276 were assigned to receive placebo (control group). The median age in both groups was 69 years; subjects were more often men and predominantly white, with good health status at the start of the study (Table). More than 95% of enrolled subjects in both groups completed the study, with 95.3% (n=18,359) in the group receiving active vaccine and 95.2% (n=18,357) in the control group completing the closeout interview.

**Outcomes**

**Confirmed Cases of Herpes Zoster**—Among the study population, 1308 subjects had suspected herpes zoster; 481 of these subjects were in the group receiving the active vaccine, and 827 were in the control group. Of the suspected cases, 984 cases (75.2%) were confirmed to be herpes zoster; however, 24 cases occurring within 30 days of vaccination and 3 repeated zoster cases were dropped in keeping with the study protocol. The population analyzed for efficacy included the remaining 957 cases (315 subjects who received active treatment and 642 subjects who received placebo).

Antiviral treatment was used in comparable numbers of patients with confirmed zoster in both groups (87.3% of vaccine recipients and 85.7% of placebo recipients). Additionally, antiviral medication use within the first 72 hours after the onset of rash was similar in the group receiving vaccine and the group receiving placebo (64.1% and 65.9%, respectively).
**Burden of Illness**—Among subjects receiving the active zoster vaccine, the primary outcome of herpes zoster BOI was significantly reduced compared with that among subjects receiving placebo therapy ($P<.001$) (Figure 1). The 61.1% reduction (95% confidence interval, 51.1-69.1) met the prespecified criteria for success.

When subjects were stratified according to age or sex, the vaccine was slightly more effective in the younger age group of those enrolled. The difference, however, did not reach statistical significance, with efficacy being established in individuals aged 60 to 69 years as well as in those older than 70 years.

Additionally, the incidence of herpes zoster was significantly reduced by 51.3% ($P<.001$) in the active treatment group compared with the control group, with an incidence of 5.42 per 1000 person-years versus 11.12 per 1000 person-years, respectively. This effect was driven substantially more by the response in the 60- to 69-year-old age group, in whom the incidence of zoster declined by 63.9% compared with 37.6% among the population aged 70 years or older. However, severity of herpes zoster disease was substantially reduced in older subjects, thus contributing to the reduction in overall burden of disease, which was the primary end point of the study. In addition, when the severity of illness was measured by affected dermatomal region—including the ophthalmic, trigeminal, cervical, thoracic, lumbar, and sacral regions—treatment with the active vaccine was associated with reduced severity of illness in each affected region.

**Postherpetic Neuralgia**
The secondary outcome in this study was the impact of active vaccine versus placebo on the rate of PHN among subjects with confirmed herpes zoster disease. In total, there were 107 cases of PHN among study subjects: 27 in the vaccine group and 80 in the placebo group. The vaccine efficacy for PHN was 66.5%, a reduction in PHN events from 1.38 to 0.46 cases per 1000 person-years ($P<.001$). There were no significant differences in rates when subjects were evaluated by age or sex. In a time-to-event analysis carried out to establish the durability of the vaccine’s protection against herpes zoster and its complications, the incidence of PHN remained significantly lower with vaccine treatment compared with placebo out to 5 years (Figure 2).

**Safety**
Overall, the number and types of serious adverse events were similar whether subjects received placebo or active vaccine. Varicella-like rashes at the injection site were more common among vaccine-treated subjects ($P<.05$), whereas rashes at other body sites occurred with equal frequency in both groups. There were five serious adverse events considered possibly related to the vaccine, though only two of these occurred in patients who received active treatment compared with three in the placebo group. A similar number of deaths occurred in both groups.

During the 42 days post injection, seven cases of confirmed zoster were recorded in the vaccine group compared with 24 occurring among placebo recipients. These results represent a significant reduction for vaccine versus placebo ($P<.05$). Importantly, vaccine-type VZV DNA was not found in any patients who had confirmed zoster at any point in the study, indicating that vaccination did not cause herpes zoster.

An adverse event substudy involving 3345 patients receiving vaccine and 3271 receiving placebo was carried out for the purpose of a more intensive safety evaluation via daily logs for adverse events, a report card of symptoms for 42 days after injection, and follow-up for subsequent hospitalizations. In this subpopulation, though rash as a reaction at the injection site was more common in the study group (10 vs 3 in the control group), the proportion of subjects with one or more systemic adverse events was similar in the two groups (24.7% in the study group vs 23.6% in the control group). Hospitalization rates were similar for both groups, and none of the hospitalizations were considered related to the vaccine.

**Indications for Use**
The zoster vaccine is indicated for the prevention of herpes zoster in adults aged 60 years and older. It is contraindicated in individuals who are...
immunocompromised because of leukemia, lymphoma, malignant neoplasms of the bone marrow or lymphatic system, because of AIDS, or because of receiving high doses of corticosteroids. The Advisory Committee on Immunization Practices to the Centers for Disease Control and Prevention recommends that the vaccine be given to all immunocompetent adults aged 60 years or older, including those who have had previous episodes of herpes zoster.20

Role for Vaccine in Preventing Herpes Zoster and Its Complications

The positive outcomes among vaccine-treated individuals suggest that the herpes zoster vaccine boosts CMI, thereby protecting vaccinated subjects against reactivation of VZV lying dormant in the dorsal root ganglion. If appropriately implemented, the zoster vaccine could prevent the occurrence of as many as a quarter of a million cases of zoster in US adults 60 years of age and older.17 The vaccine would also significantly reduce the BOI in others in whom herpes zoster develops after vaccination by resulting in less severe acute herpes zoster as well as decreased incidence of PHN. Furthermore, the prevention of herpes zoster reaps wider benefits in terms of reduced morbidity associated with the disease. Although the SPS study evaluated only the impact of the vaccine on the development of PHN, one can deduce—if only from its preventive potential against the onset of herpes zoster—that the vaccine should significantly reduce the risk for those from other potential complications, including herpes zoster ophthalmicus.

Herpes zoster leads to substantial morbidity among the elderly. Although the incidence of herpes zoster is relatively low in young people, with an annual incidence among immunocompetent adults of 1.5 to 3.0 cases per 1000 person-years, rates of occurrence increase greatly after age 50 years.13,21,22 The pain of herpes zoster or its complications, including herpes zoster ophthalmicus, can have an extremely negative impact on quality of life, interfering with sleep, energy levels, mood, and other aspects of life.23,24 Also, herpes zoster leads to high rates of hospitalization among older individuals, with each hospitalization for herpes zoster costing approximately $15,583, according to 1995 data, likely an underestimate by today’s costs.25 Much advantage is to be gained by preventing herpes zoster and protecting the elderly against its potentially chronic and debilitating course.

Comment

The SPS established the ability of the new zoster vaccine to prevent herpes zoster and its most common complication, PHN, and to reduce the severity of herpes zoster in adults aged 60 years or older. The Advisory Committee on Immunization Practices recommends the use of the herpes zoster vaccine in all adults aged 60 years or older. Based on the results of the SPS, the vaccine promises to significantly reduce the health and economic burden of illness associated with herpes zoster disease in the United States.26 However, these benefits will not be attained unless physicians and other healthcare providers actively educate their patients about the disease and offer the vaccine to appropriate individuals. In addition, older adults must accept the vaccine and avail themselves of its use. Through these combined efforts, reduction of herpes zoster and its complications can become a reality.

References


