SUPPLEMENT ARTICLE

Vaccination against Herpes Zoster and Postherpetic Neuralgia

Michael N. Oxman,[1,2] Myron J. Levin,[3] and the Shingles Prevention Study Group[a]

[1]VA San Diego Healthcare System, San Diego, and [2]University of California, San Diego, California; [3]University of Colorado Health Sciences Center, Denver

Background. Herpes zoster (HZ) and postherpetic neuralgia (PHN) cause significant morbidity in older adults. The incidence and severity of HZ and PHN increase with age in association with an age-related decline in varicella-zoster virus (VZV)–specific cell-mediated immunity (VZV-CMI). VZV vaccines can boost VZV-CMI. Therefore, we tested the hypothesis that VZV vaccination would protect older adults against HZ and PHN.

Methods. We enrolled 38,546 adults ⩾60 years of age in a randomized, double-blind, placebo-controlled trial of an investigational HZ vaccine and actively followed subjects for the development of HZ. The primary end point was the burden of illness due to HZ (HZ BOI), a composite measure of the incidence, severity, and duration of pain and discomfort caused by HZ. The secondary end point was the incidence of PHN.

Results. Subject retention was >95%. HZ vaccine reduced the HZ BOI by 61.1% (95% confidence interval [CI], 51.1%–69.1%; $P < .001$) and reduced the incidence of PHN by 66.5% (95% CI, 47.5%–79.2%; $P < .001$). The incidence of HZ was also reduced by 51.3% (95% CI, 44.2%–57.6%; $P < .001$). HZ vaccine was well tolerated; injection site reactions were generally mild. HZ vaccine neither caused nor induced HZ.

Conclusion. The Shingles Prevention Study demonstrated that HZ vaccine significantly reduced the morbidity due to HZ and PHN in older adults.

Herpes zoster (HZ), or shingles, is a disease of the sensory ganglion, nerves, and skin that results from reactivation of varicella-zoster virus (VZV) that has remained latent within sensory neurons after primary VZV infection (i.e., varicella, or chickenpox) [1–4]. HZ is characterized clinically by unilateral radicular pain and a vesicular rash that is generally limited to a single dermatome [1–6]. Neuropathic pain, likely due to neuronal damage and inflammation resulting from the multiplication and spread of the reactivated VZV, is a major manifestation of HZ, especially in older persons [1, 5–9]. The dermatomal HZ rash is frequently preceded by neuropathic pain; neuropathic pain usually accompanies the rash; and neuropathic pain and discomfort (e.g., allodynia and severe pruritus) may persist or develop after the dermatomal rash has healed—a debilitating complication of HZ known as "postherpetic neuralgia" (PHN) [5–7, 9–15]. The pain and discomfort associated with HZ can be prolonged and disabling, severely compromising the patient's quality of life and capacity to carry out activities of daily living [16].

The frequency and severity of HZ and PHN increase with increasing age; more than half of all recognized cases of HZ and most cases of clinically significant PHN occur in immunocompetent persons ⩾60 years of age [2–6, 9–15, 17]. Antiviral therapy reduces the duration and severity of HZ, but it does not prevent PHN [4, 9, 14, 15, 18–20]. PHN may persist for months or even years, and it is often refractory to treatment [19]. Thus, some means of preventing HZ and PHN is needed to reduce the burden of these painful conditions on older

Potential conflicts of interest: M.N.O. is Study Chairman of Department of Veterans Affairs (VA) Cooperative Study #403, The Shingles Prevention Study, and its substudies, which have been supported, in part, by grants from Merck to the VA Cooperative Studies Program, The VA San Diego Medical Research Foundation, and the VA Connecticut Research and Education Foundation. M.J.L. has received lecture fees and honoraria, consultation fees, and research support from Merck; holds a partial interest in a patent related to the herpes zoster vaccine; and is on the Merck speakers' bureau.

Financial support: The Shingles Prevention Study, VA Cooperative Study #403, was conducted by the Cooperative Studies Program, Department of Veterans Affairs, Office of Research and Development in collaboration with the National Institute of Allergy and Infectious Diseases and Merck. Additional support was provided by a grant from Merck to the VA Cooperative Studies Program and by the James R. and Jesse V. Scott Fund for Shingles Research. Supplement sponsorship is detailed in the Acknowledgments.

[a] Members of the Shingles Prevention Study Group are listed after the text.

Reprints or correspondence: Dr. Michael N. Oxman, The Shingles Prevention Study (111F-1), VA Medical Center, 3350 La Jolla Village Dr., San Diego, CA 92161 (mnoxman@ucsd.edu).

The Journal of Infectious Diseases 2008; 197:S228–36

0022-1899/2008/19705S2-0035$15.00
DOI: 10.1086/522159

persons, who constitute a growing proportion of the populations of most developed countries [21–23].

In 1965, after 16 years of careful surveillance for varicella and HZ among the patients in his medical practice, Edgar Hope-Simpson published his seminal observations and a remarkably prescient hypothesis [3]. He observed that the incidence and severity of HZ increased with increasing age and hypothesized that this was due to an age-related decline in immunity to VZV. Hope-Simpson also observed that recurrences of HZ were relatively uncommon among immunocompetent persons (in contrast to the frequent recurrences of herpes simplex), and he hypothesized that this was because an episode of HZ induced an increase in immunity to VZV sufficient to "immunize" against a subsequent episode [3, 21]. Observations during the past 4 decades have supported the thesis that T cell–mediated immunity to VZV (VZV-CMI) is the major determinant of the risk and severity of HZ [2, 9, 21, 24–32]. The increased incidence and severity of HZ and PHN observed in older adults are closely correlated with a progressive age-related decline in VZV-CMI, whereas levels of antibody to VZV remain relatively constant with increasing age [2, 9, 21, 24, 27–32].

The development by Takahashi and his colleagues of the live attenuated Oka strain of VZV in the early 1970s made it possible to immunize VZV-naive children and adults against varicella [33–36] and to explore the possibility of boosting VZV-CMI in older adults [21, 31]. Subsequent studies have demonstrated that Oka-derived VZV vaccines can elicit a significant increase in VZV-CMI in immunocompetent older adults [32, 37–39] and can reduce the incidence and severity of HZ in recipients of bone marrow allografts [40, 41]. These observations led us to hypothesize that immunization of older adults with live attenuated Oka VZV vaccine would boost their waning VZV-CMI and thereby provide protection against HZ and PHN [21, 31, 42, 43]. The Shingles Prevention Study (SPS), Department of Veterans Affairs Cooperative Study #403, was initiated to test this hypothesis by determining whether vaccination with an investigational live attenuated Oka/Merck VZV vaccine would decrease the incidence and/or severity of HZ and PHN in immunocompetent adults ⩾60 years of age. The results of the SPS presented here have been published elsewhere [18].

STUDY DESIGN AND METHODS

The SPS was a placebo-controlled, double-blind, multicenter trial in which adults ⩾60 years of age were randomized to receive either VZV vaccine or placebo in a 1:1 ratio at 22 study sites across the United States. Randomization was stratified by study site and age group, 60–69 and ⩾70 years of age. The SPS was approved by a Department of Veterans Affairs Cooperative Studies Program Human Rights Committee and all local institutional review boards. All subjects provided written informed consent.

The design and execution of the SPS presented several major challenges (listed in the Appendix). Enrollment of a large number of subjects proved to be more difficult than anticipated. However, with the aid of local outreach, media coverage, advertising, and letters to households with ⩾1 members ⩾60 years of age in zip codes around each study site, 38,546 subjects were enrolled in the SPS between November 1998 and September 2001. Eligible subjects were required to have a history of varicella or at least 30 years of residence in the continental United States, to be ⩾60 years of age, and to give written informed consent. Exclusion criteria included immunosuppression resulting from diseases or their treatment, prior HZ or varicella vaccination, hypersensitivity to components of the investigational vaccine/placebo, receipt of blood products within 3 months before or planned during the study period, receipt of live vaccines within 1 month or inactivated vaccines within 2 weeks before randomization, concurrent antiviral therapy, or any condition that the investigator believed might interfere with the trial. Subjects who developed HZ were offered famciclovir without cost in accordance with the protocol-specified HZ follow-up procedure and received treatment for pain prescribed by SPS physicians.

At enrollment, subjects were educated about the signs and symptoms of HZ and instructed to contact their study site immediately for evaluation by a SPS physician if they developed a new rash or unilateral pain syndrome. To ensure capture of mild or vaccine-modified cases of HZ, study personnel maintained a low threshold for evaluating subjects with new rashes and for classifying subjects as "suspected cases of HZ." Active follow-up and case ascertainment were ensured by an interactive automated telephone response system (ATRS) developed and validated for the SPS. Subjects were instructed to call the toll-free ATRS number on a specific day each month. If their responses to a standardized set of questions suggested possible HZ, they were instructed to immediately contact their local study site, and a fax containing their responses was sent to the site. The ATRS also reminded subjects to report HZ-like rashes to the study site as soon as they occurred. Subjects who did not call the ATRS within a preestablished time interval were called by the ATRS. If this failed, the ATRS transmitted a fax prompting the local study site to contact the subject directly. The ATRS handled 86% of subject follow-up, permitting SPS personnel to focus on retention of subjects at risk of being lost to follow-up. This resulted in retention and follow-up of >95% of the enrolled subjects through the end of the study. Closeout interviews with each subject did not reveal any missed cases of HZ.

Development of a quantitative measure of severity for cases of HZ was problematic because pain and discomfort are the major cause of morbidity in older persons with HZ, and these symptoms are subjective. Accordingly, we developed and val-

idated an HZ-specific assessment tool, the Zoster Brief Pain Inventory (ZBPI), that captured HZ pain and discomfort, including unpleasant sensations, such as allodynia and pruritus, that are not always characterized as pain by persons with HZ [44]. The ZBPI, administered to subjects at specified intervals over a 182-day observation period, asked subjects to rate their level of HZ-associated pain and discomfort at its "worst," "average," and "least" in the past 24 h and "right now" on a 0–10 rating scale. The "worst pain in the last 24 h" score was chosen as the end point measurement because it had the greatest reliability and was highly correlated with the ZBPI average pain score and other validated pain measures [44, 45]. For each evaluable case of HZ, the ZBPI data were used to calculate an "HZ Severity-of-Illness Score," defined as the area under the ZBPI "worst pain" response–versus–time curve during this 182-day period (figure 1). Increasing mean HZ Severity-of-Illness Scores have been shown to be highly correlated with decreasing health-related quality of life and functional status in older adults [44]. The HZ Severity-of-Illness Score was defined as 0 for subjects who did not develop HZ during the study.

The primary SPS end point was the burden of illness caused by HZ (HZ BOI), a severity-by-duration measure representing the total HZ-associated pain and discomfort in a population of study subjects [16, 44, 46]. The HZ BOI is the sum of the HZ Severity-of-Illness Scores of all members of the group (vaccine recipients or placebo recipients). This end point measures any effect of the HZ vaccine on the incidence of HZ and/or the severity and/or duration of HZ pain and discomfort (figure 2).

The secondary SPS end point was the incidence of clinically significant PHN, defined as HZ-associated pain or discomfort rated as ≥ 3 (on a 0–10 scale) persisting or appearing >90 days after HZ rash onset. Scores <3 are not associated with significant decrements in quality of life or ability to carry out activities of daily living and, thus, were not considered to represent clinically significant PHN [10, 44].

The incidence of HZ was also determined in vaccine and placebo recipients.

To determine "evaluable cases of HZ" for the analysis of vaccine efficacy, each suspected case of HZ was classified as an "evaluable case of HZ" or "not a case of HZ" before unblinding, by use of a hierarchical algorithm that incorporated the results of a central polymerase chain reaction (PCR) assay, local virus culture, and the final clinical diagnosis established by a clinical evaluation committee (CEC) [18].

A real-time PCR assay, developed and validated for the SPS, employed 2 sets of primers and a probe from VZV gene 62 to detect and discriminate between DNA from wild-type and Oka vaccine strains of VZV on the basis of a single-base-pair difference and the preferential amplification of the target by homologous primers. Another set of primers and probe was used to detect herpes simplex virus (HSV) DNA. Each primer pair and its probe was run in individual PCRs, together with positive and negative controls and viral and human β-globin DNA standards. Assay sensitivity was sufficient to detect ~13 copies of wild-type or vaccine-strain VZV DNA. Every PCR for viral DNA detection was multiplexed with primers and a probe for the human β-globin gene to demonstrate adequacy of the specimen by detecting cellular DNA (R. Harbecke, P. M. Keller, and M.N.O., unpublished data).

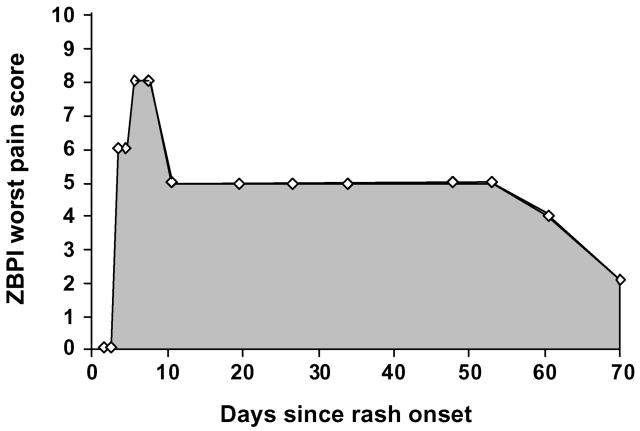

Figure 1. Herpes Zoster (HZ) Severity-of-Illness Score. This is an example of the HZ Severity-of-Illness Score for a hypothetical subject with HZ. The HZ Severity-of-Illness Score is defined as the area under the curve of Zoster Brief Pain Inventory (ZBPI) "worst pain in the last 24 h" scores over time during the 182-day period after HZ rash onset.

Although not required by the SPS protocol, viral culture was performed by local laboratories at some study sites.

The CEC, a group of 5 study physicians with HZ expertise, evaluated all suspected cases of HZ identified during the study. Each CEC member provided a clinical diagnosis for each suspected case of HZ after independently reviewing a summary of the rash and pain evaluations, digital photographs of the subject's rash, and progress notes documenting the course of illness. CEC members were blinded to treatment assignment and laboratory results. A unanimous diagnosis of "HZ" or "not HZ" by the CEC members constituted a final clinical diagnosis. CEC members discussed each nonunanimous case and determined the final clinical diagnosis by majority vote. Individual CEC members did not evaluate cases from their respective study sites.

If the PCR assay revealed VZV DNA, the case was classified as an "evaluable case of HZ"; if the PCR assay was negative for VZV DNA but positive for β-globin or HSV DNA, the case was classified as "not a case of HZ." If the PCR specimen was "inadequate" (i.e., negative for both virus and β-globin DNA) or missing, isolation and confirmation of VZV or HSV in the local virology laboratory, if available, was used to establish the

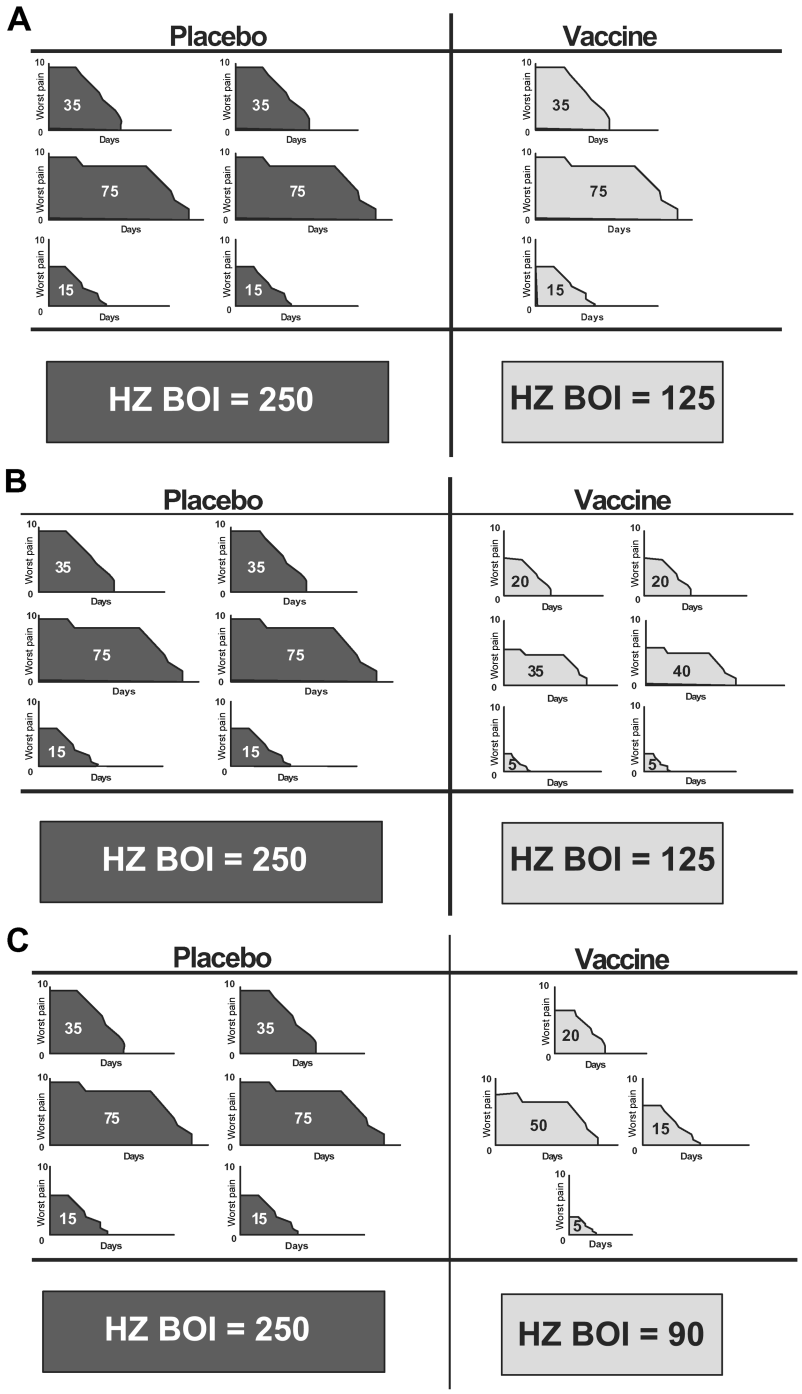

Figure 2. Diagrams illustrating the behavior of the herpes zoster (HZ) Burden of Illness (HZ BOI) under 3 different theoretical circumstances. *A,* Behavior of the HZ BOI if the HZ vaccine were to reduce the incidence but not the severity of HZ, in which case there would be fewer cases of HZ in the vaccine recipients than in the placebo recipients, but the cases of HZ in the vaccine recipients would have, on average, HZ Severity-of-Illness Scores comparable to those of the cases in placebo recipients. *B,* Behavior of the HZ BOI if the HZ vaccine were to reduce the severity but not the incidence of HZ, in which case there would be just as many cases of HZ in the vaccine recipients as in the placebo recipients, but the cases of HZ in the vaccine recipients would have, on average, lower HZ Severity-of-Illness Scores than those in the placebo recipients. *C,* Behavior of the HZ BOI if the HZ vaccine were to reduce both the incidence and the severity of HZ, in which case there would be fewer cases of HZ in the vaccine recipients then in the placebo recipients, and the cases of HZ in the vaccine recipients would have, on average, lower HZ Severity-of-Illness Scores than those in the placebo recipients. In all 3 situations, the HZ BOI would be lower in the vaccine recipients than in the placebo recipients. The figures shown for the HZ Severity-of-Illness Scores and for the HZ BOI are for purposes of illustration only.

diagnosis. In the absence of a valid laboratory diagnosis, the case was classified on the basis of the final clinical diagnosis by the CEC.

All serious adverse events (SAEs) were actively ascertained during the first 42 days after vaccination and passively ascertained thereafter. Deaths were identified by reports from the families of subjects and during follow-up of missed ATRS calls. Approximately 6600 subjects (~300 per study site) were enrolled in an Adverse Events (AE) Substudy. These subjects maintained a daily log of body temperature and a report card of clinical complaints during the first 42 days after vaccination. During the remainder of the study, subjects in the AE Substudy were actively followed to identify all hospitalizations.

RESULTS

Study subjects. A total of 38,546 subjects were enrolled between November 1998 and September 2001; 19,270 received HZ vaccine, and 19,276 received placebo. The median age in both groups was 69 years; 6.6% of the vaccine recipients and 6.9% of the placebo recipients were ⩾80 years of age. Forty-one percent of the subjects in the vaccine and placebo groups were female. At enrollment, most subjects had no (51.3%) or mild (38.6%) health limitations on their activities. The mean duration of HZ surveillance was 3.13 years (median, 3.12 years), with no difference between the vaccine and placebo groups. More than 95% of enrolled subjects were actively followed to the end of the study and completed a closeout interview. Only 0.6% withdrew or were lost to follow-up; 4.1% died before the study ended [18].

Evaluable cases of HZ. A total of 1308 suspected cases of HZ were evaluated; 317 subjects with rashes (156 in the vaccine group; 161 in the placebo group) were determined not to have HZ. Except for 49 of these that were caused by HSV (24 in vaccine recipients and 25 in placebo recipients), no specific alternative diagnosis was established for suspicious rashes determined not to be HZ. Study closeout interviews did not identify any missed cases of HZ. The final diagnosis in 1156 (88.4%) of the 1308 suspected cases of HZ (417 in vaccine recipients; 739 in placebo recipients) was based on the results of the PCR assay. Of the 1308 suspected cases, 984 (75.2%) were determined to be evaluable cases of HZ. Of these, 24 were excluded from the primary efficacy analysis per protocol because they occurred within 30 days of vaccination (6 in vaccine recipients and 18 in placebo recipients), and 3 were excluded because they represented a subject's second case of HZ (1 in a vaccine recipient and 2 in placebo recipients). The remaining 957 evaluable cases of HZ (315 in vaccine recipients; 642 in placebo recipients) constituted the end points for the efficacy analysis. In each group, >93% of the subjects with HZ were positive for wild-type VZV DNA by PCR assay. Vaccine virus was never detected [18].

HZ burden of illness. The HZ vaccine significantly reduced the HZ BOI Score (average HZ Severity-of-Illness Score among all vaccine versus placebo recipients) ($P < .001$) (figure 3). Overall, vaccine efficacy for the HZ BOI (VE_{BOI}) was 61.1% (95% confidence interval [CI], 51.1%–69.1%), which met the prespecified criteria for success. There were no significant differences in VE_{BOI} by sex or by age stratum, although VE_{BOI} appeared to be slightly lower in the older subjects (figure 3). Moreover, the mean HZ Severity-of-Illness Score among evaluable cases of HZ was significantly lower among vaccine recipients than among placebo recipients (141.2 vs. 180.5; $P = .008$). For virtually every level of HZ Severity-of-Illness Score, fewer cases were seen in the vaccine group than in the placebo group; this was especially notable for cases with higher scores—that is, cases with more painful and protracted disease [18]. For example, HZ Severity-of-Illness Scores >600, equivalent to >60 days of "the worst pain imaginable," were observed in only 11 vaccine recipients, compared with 40 placebo recipients, which represents a 79% reduction in the HZ vaccine recipients (data not shown).

The use of antiviral medications in evaluable cases of HZ

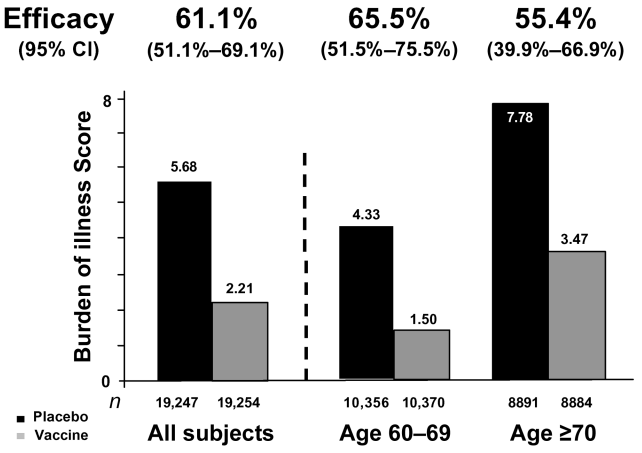

Figure 3. Herpes zoster (HZ) vaccine efficacy for the HZ Burden of Illness (HZ BOI). The primary end point of the Shingles Prevention Study was the HZ BOI, a severity-by-duration measure of the total pain and discomfort associated with HZ in the population of study subjects. For each confirmed case of HZ, responses to the "worst pain in the last 24 h" question in the Zoster Brief Pain Inventory were used to calculate an HZ Severity-of-Illness Score, defined as the area under the curve of HZ pain and discomfort plotted against time during the 182-day period after the onset of HZ rash. Subjects with HZ had HZ Severity-of-Illness Scores ranging from 0 to 1813. Increasing HZ Severity-of-Illness Scores are highly correlated with a decrease in the health-related quality of life and in functional status of older adults [44]. An HZ Severity-of-Illness Score of 0 was recorded for subjects in whom HZ did not develop during the study period. The HZ BOI Score represents the average HZ Severity-of-Illness Score among all subjects in the vaccine or placebo groups; it was calculated as the sum of the HZ Severity-of-Illness Scores of all members of a group divided by the total no. of subjects in the group. The figure is based on data published in [18].

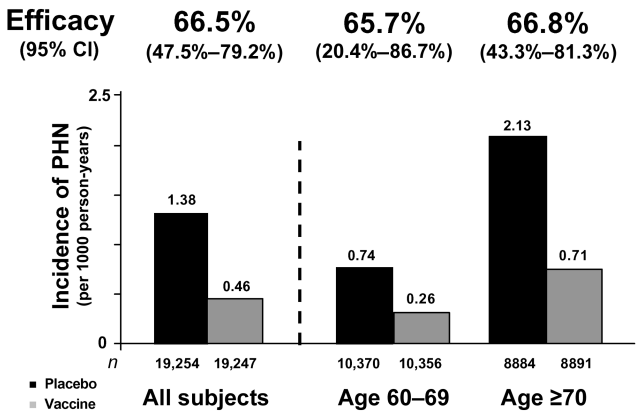

Figure 4. Herpes zoster (HZ) vaccine efficacy for the incidence of postherpetic neuralgia (PHN). HZ vaccine significantly reduced the incidence of PHN, by approximately two-thirds, in all subjects and in both age strata. It is important to note that this reduction is among all subjects and not just those with HZ. The figure is based on data published in [18].

was comparable in vaccine and placebo recipients (87% and 86%, respectively) and was initiated within 72 h of HZ rash onset in 64% of vaccine recipients and 66% of placebo recipients [18]. The frequency of pain medication use was comparable in the vaccine and placebo recipients who developed HZ (acetaminophen, 44% and 46%, respectively; anticonvulsants, 9% and 12%; corticosteroids, 3% and 3%; nonsteroidal anti-inflammatory drugs, 41% and 42%; opiates, 44% and 42%; tricyclic antidepressants, 5% and 6%), whereas the average duration and quantity of opiate usage were lower by 38% and 42%, respectively, in the vaccine recipients who developed HZ.

Incidence of PHN. There were 107 cases of PHN; 27 among vaccine recipients and 80 among placebo recipients (0.46 vs. 1.38 cases/1000 person-years, respectively; $P < .001$) (figure 4). Overall, vaccine efficacy for PHN (VE_{PHN}) was 66.5% (95% CI, 47.5%–79.2%), which met the prespecified criteria for success. There were no significant differences in VE_{PHN} by sex or by age stratum (figure 4). In fact, there was no decrease in VE_{PHN} in the older subjects. The VE_{PHN} did not change appreciably when PHN was defined using alternate cutoff times for duration of pain (from >1 month to >6 months after rash onset) [18].

Incidence of HZ. Although not a primary or secondary end point, the incidence of HZ per 1000 person-years was significantly reduced by the HZ vaccine, from 11.1 in placebo recipients to 5.4 in vaccine recipients ($P < .001$) (figure 5). Vaccine efficacy for the incidence of HZ (VE_{HZ}) was 51.3% (95% CI, 44.2%–57.6%); VE_{HZ} was significantly higher in the younger age stratum than in the older age stratum (figure 5) [18].

Vaccine safety. In the total SPS population, death rates over the entire study period were comparable in the vaccine and placebo recipients (4.1% in each group). During the first 42 days after vaccination, the proportion of vaccine and placebo subjects with ⩾1 SAE was also similar (1.4% in each group), as was the distribution of SAEs by organ system (data not shown). During this period, injection-site rashes were significantly more frequent in the vaccine group than in the placebo group, but rashes at other locations occurred at similar rates in each group. During the first 42 days after vaccination, there were 7 evaluable cases of HZ in vaccine recipients and 24 in placebo recipients. During the entire study, 5 subjects experienced SAEs that were assessed by the study site investigators as being "possibly vaccine-related." Two had received vaccine: a 64-year-old woman with exacerbation of asthma on day 2 after vaccination and an 80-year-old man with a diagnosis of polymyalgia rheumatica on day 3 after vaccination. Three had received placebo: a 65-year-old man with an anaphylactoid reaction 90 min after vaccination (and 30 min after eating peanuts), a 69-year-old man with a diagnosis of polymyalgia rheumatica on day 15 after vaccination, and a 78-year-old man with a diagnosis of Goodpasture syndrome on day 52 after vaccination [18].

In the AE substudy, significantly more subjects in the vaccine group had ⩾1 AE of any type than in the placebo group, reflecting a greater frequency of injection-site AEs in vaccine recipients. The most frequent injection-site AEs reported by vaccine recipients were erythema (36%), pain or tenderness (35%), swelling (26%), and pruritus (7%). In contrast, the proportion of subjects with ⩾1 systemic AE was similar in the vaccine and placebo recipients. During the postvaccination period, significantly more AE Substudy subjects in the vaccine group than in the placebo group experienced ⩾1 SAE (1.9% vs. 1.3%, respectively; $P = .034$); there were no significant differences in the distribution of SAEs by body system or event (data not shown). A post hoc, subject-by-subject review re-

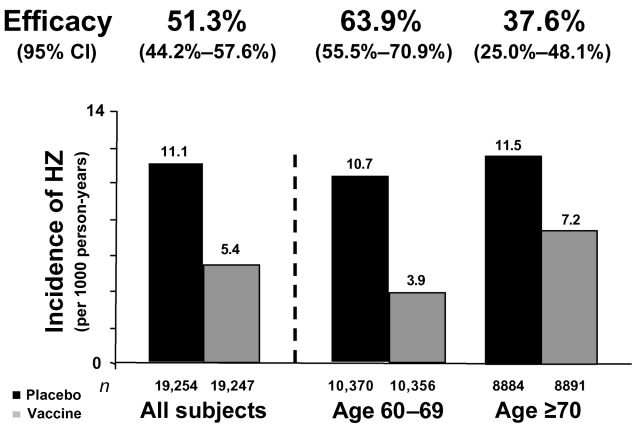

Figure 5. Herpes zoster (HZ) vaccine efficacy for the incidence of HZ. HZ vaccine significantly reduced the overall incidence of HZ, by 51.3%, although vaccine efficacy for the incidence of HZ was reduced substantially in subjects ⩾70 years of age. The figure is based on data published in [18].

vealed no clinically meaningful differences between treatment groups in the pathophysiology, nature, timing, intensity, or outcome of these events [18]. Subjects in the AE Substudy were monitored for hospitalizations from the day of vaccination to the end of study. The number of subjects with ⩾1 hospitalizations was similar for the vaccine and placebo groups (0.2% in each). No hospitalization in either group was assessed as being vaccine related [18].

DISCUSSION

HZ and PHN cause significant morbidity in older adults [14–17, 19, 44]. It is estimated, on the basis of current US population figures and data on the age-specific incidence, that there are a million or more new cases of HZ each year in the United States, a number that is likely to increase as the population ages. Antiviral therapy does not eliminate the morbidity of HZ and PHN [4, 9, 15, 19, 20], and the neuropathic pain of PHN is often refractory to treatment [19]. Thus, a means of prevention would offer significant medical and economic benefit.

The SPS demonstrated that an investigational HZ vaccine reduced the HZ BOI in people ⩾60 years of age by >60% [18]. The HZ BOI was chosen as the primary SPS end point because it is sensitive to changes in the incidence, severity, and duration of HZ pain and discomfort [16, 44, 46]. The HZ vaccine also reduced the incidence of PHN, the most common debilitating complication of HZ, by 66.5% [18]. Comparable efficacy with respect to PHN was demonstrated in both age strata, with a trend toward greater efficacy for PHN of longer duration. The vaccine showed significant efficacy for both end points in both age strata and in both sexes [18]. Further analysis of the vaccine's effect on the components of the HZ BOI showed that it reduced the overall incidence of HZ by 51.3% and significantly reduced the average severity of illness among subjects who developed HZ [18]. The comparable usage of antivirals by vaccine and placebo recipients who developed HZ and the lower average usage of opiates by the vaccine recipients indicate that the treatment administered to subjects who developed HZ did not bias the study results in favor of HZ vaccine.

The SPS confirmed the increased incidence and severity of HZ in older individuals, which is associated with a progressive age-related decline in VZV-CMI [3, 18, 21, 26–32]. Because recent studies, as well as data from individuals in the SPS, indicate that VZV vaccines can boost VZV-CMI in older individuals [21, 32, 37–39], we believe that the observed efficacy of the investigational HZ vaccine reflects its ability to boost VZV-CMI in vaccinated subjects. The investigational HZ vaccine was well tolerated. In the entire study population, rates of SAEs, systemic AEs, hospitalizations, and deaths were low and comparable in the vaccine and placebo groups, and local reactions at the vaccination site were generally mild.

The capacity of the HZ vaccine to protect against HZ may have added significance if, as has been hypothesized by some investigators, the elimination of varicella by universal childhood vaccination results in an accelerated loss of VZV-CMI in adults no longer exposed to children with varicella and a corresponding increase in the age-specific incidence of HZ [47, 48].

Several features of the SPS are noteworthy. Monthly contact with subjects, facilitated by the ATRS, permitted active surveillance for HZ, helped to retain >95% of the 38,546 enrolled subjects in the SPS, ensured the identification and evaluation of all cases of HZ that occurred (including mild and atypical cases), and supported the evaluation of vaccine safety. The sensitive and specific PCR assay for VZV and HSV DNA, developed and validated for the SPS, established the diagnosis in 88.4% of the suspected cases of HZ and in 93.4% of the evaluable cases of HZ in the study.

THE SHINGLES PREVENTION STUDY GROUP

The Shingles Prevention Study was planned and/or administered by a Planning/Executive Committee: Michael N. Oxman (Chair), Robert D. Arbeit, Patricia Barry, Chris Beisel, Kathy D. Boardman, Cindy L. Colling, Larry E. Davis, Lawrence D. Gelb, Anne A. Gershon, Anthony R. Hayward, Michael R. Irwin, Gary R. Johnson, Myron J. Levin, Peter N. Peduzzi, Kenneth E. Schmader, Michael S. Simberkoff, Stephen E. Straus, Adriana Weinberg, Heather M. Williams, Paula Annunziato, Christina Y. Chan, Ivan S. F. Chan, and Jeffrey L. Silber

The VA Cooperative Studies Program Shingles Prevention Study Investigators include the following individuals: L. E. Davis (Albuquerque, NM); C. A. Kauffman (Ann Arbor, MI); S. K. Keay (Baltimore, MD); A. R. Marques, N. E. Soto, and P. Brunell (Bethesda, MD); J. W. Gnann (Birmingham, AL); R. Serrao, D. J. Cotton, R. P. Goodman, and R. D. Arbeit (Boston, MA); C. T. Pachucki (Hines, IL); M. J. Levin (Denver, CO); K. E. Schmader (Durham, NC); W. A. Keitel (Houston, TX); R. N. Greenberg (Lexington, KY); V. A. Morrison (Minneapolis, MN); P. F. Wright and M. R. Griffin (Nashville, TN); M. S. Simberkoff (New York, NY); S. S. Yeh and Z. Lobo (Northport, NY); M. Holodniy and J. Loutit (Palo Alto, CA); R. F. Betts (Rochester, NY); L. D. Gelb (St. Louis, MO); G. E. Crawford (San Antonio, TX); J. Guatelli and P. A. Brooks (San Diego, CA); K. M. Neuzil (Seattle, WA); and J. F. Toney (Tampa, FL).

Administrative and statistical support was provided by the VA Cooperative Studies Program Coordinating Center, West Haven, Connecticut: P. Antonelli, B. Huff, J. H. Zhang, T. C. Kyriakides, K. Newvine, R. Concepcion, K. DiBenedetto, S. O'Neil, and P. O'Brien.

Clinical research pharmacy management was provided by the VA Cooperative Studies Program Clinical Research Pharmacy Coordinating Center, Albuquerque, New Mexico: K. D. Boardman, J. Peterson, and B. Del Curto.

Central Laboratory services were provided by the Denver

Central Cell-Mediated Immunity Laboratory, Denver, Colorado: D. Elizabeth, L. Enomoto, and M. Jones; by the San Diego Central Cell-Mediated Immunity Laboratory: H. A. Stanley and P. Jordan; and by the San Diego Central Diagnostic Laboratory: R. Harbecke, Y. Naidu, and L. J. Wopschall.

Statistical assistance at Merck was provided by I. S. F. Chan, W. W. B. Wang, J. Xu, J. Heyse, and H. Matthews. Clinical administration at Merck was provided by J. Ryan, J. Eiden, F. Schödel, J. Sadoff, S. Manoff, C. J. White, R. Vessey, D. Stinson, M. E. Thompson, K. Adair, P. Brownell, K. Perrrin, S. Senior, R. Rutledge, and N. Bundick.

Acknowledgments

Supplement sponsorship. This article was published as part of a supplement entitled "Varicella Vaccine in the United States: A Decade of Prevention and the Way Forward," sponsored by the Research Foundation for Microbial Diseases of Osaka University, GlaxoSmithKline Biologicals, the Sabin Vaccine Institute, the Centers for Disease Control and Prevention, and the March of Dimes.

APPENDIX

THE SHINGLES PREVENTION STUDY: MAJOR CHALLENGES

- **Enrollment** of a large number of subjects at increased risk for herpes zoster (HZ) and postherpetic neuralgia (i.e., persons ⩾60 years of age)
- **Active follow-up** of all subjects to identify and evaluate every case of HZ occurring in the study population as soon as possible after rash onset
- Development of a **quantitative measure of HZ severity**
- Selection of a **primary end point** that would measure the impact of the HZ vaccine on the incidence, severity, and/or duration of HZ
- Determination of **evaluable cases of HZ** for the analysis of HZ vaccine efficacy

References

1. Head H, Campbell AW. The pathology of herpes zoster and its bearing on sensory localization. Brain **1900**; 23:353–523.
2. Weller TH. Varicella and herpes zoster. Changing concepts of the natural history, control, and importance of a not-so-benign virus. N Engl J Med **1983**; 309:1434–40.
3. Hope-Simpson RE. The nature of herpes zoster: a long-term study and a new hypothesis. Proc R Soc Med **1965**; 58:9–20.
4. Gnann JW Jr, Whitley RJ. Herpes zoster. N Engl J Med **2002**; 347: 340–6.
5. Oxman MN. Clinical manifestations of herpes zoster. In: Arvin AM and Gershon AA, eds. Varicella zoster virus: virology and clinical management. Cambridge, UK: Cambridge University Press, **2000**:246–75.
6. Wood MJ. Herpes zoster and pain. Scand J Infect Dis Suppl **1991**; 80: 53–61.
7. Gilden DH, Kleinschmidt-DeMasters BK, LaGuardia JJ, Mahalingam R, Cohrs RJ. Neurologic complications of the reactivation of varicella-zoster virus. N Engl J Med **2000**; 342:635–45.
8. Watson CPN, Deck JH, Morshead C, Van der Kooy D, Evans RJ. Postherpetic neuralgia: further postmortem studies of cases with and without pain. Pain **1991**; 44:105–17.
9. Kost RG, Straus SE. Postherpetic neuralgia: pathogenesis, treatment, and prevention. N Engl J Med **1996**; 335:32–42.
10. Hope-Simpson RE. Postherpetic neuralgia. J R Coll Gen Pract **1975**; 25:571–5.
11. Burgoon CF Jr, Burgoon JS, Baldridge GD. The natural history of herpes zoster. J Am Med Assoc **1957**; 164:265–9.
12. Ragozzino MW, Melton LJ 3rd, Kurland LT, Chu CP, Perry HO. Population-based study of herpes zoster and its sequelae. Medicine **1982**;61: 310–6.
13. Donahue JG, Choo PW, Manson JE, Platt R. The incidence of herpes zoster. Arch Intern Med **1995**; 155:1605–9.
14. Dworkin RH, Portenoy RK. Pain and its persistence in herpes zoster. Pain **1996**; 67:241–51.
15. Schmader K. Herpes zoster in older adults. Clin Infect Dis **2001**; 32: 1481–6.
16. Lydick E, Epstein RS, Himmelberger D, White CJ. Herpes zoster and quality of life: a self-limited disease with severe impact. Neurology **1995**; 45:S52–3.
17. Galil K, Choo PW, Donahue JG, Platt R. The sequelae of herpes zoster. Arch Intern Med **1997**; 157:1209–13.
18. 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**; 352:2271–84.
19. Dworkin RH, Schmader KE. Treatment and prevention of postherpetic neuralgia. Clin Infect Dis **2003**; 36:877–82.
20. Whitley RJ, Weiss H, Gnann JW Jr, et al. Acyclovir with and without prednisone for the treatment of herpes zoster: a randomized, placebo-controlled trial. Ann Intern Med **1996**; 125:376–83.
21. Oxman MN. Immunization to reduce the frequency and severity of herpes zoster and its complications. Neurology **1995**; 45:S41–6.
22. Kinsella K, Velkoff V. US Census Bureau series P95/01–1. An aging world: 2001. Washington, DC: US Government Printing Office, **2001**.
23. Centers for Disease Control and Prevention. Public health and aging: trends in aging—United States and worldwide. MMWR Morb Mortal Wkly Rep **2003**; 52:101–6.
24. Dolin R, Reichman RC, Mazur MH, Whitley RJ. Herpes zoster-varicella infections in immunosuppressed patients. Ann Intern Med **1978**; 89: 375–88.
25. Wilson A, Sharp M, Koropchak CM, Ting SF, Arvin AM. Subclinical varicella-zoster virus viremia, herpes zoster, and T lymphocyte immunity to varicella-zoster viral antigens after bone marrow transplantation. J Infect Dis **1992**; 165:119–26.
26. Buchbinder SP, Katz MH, Hessol NA, et al. Herpes zoster and human immunodeficiency virus infection. J Infect Dis **1992**; 166:1153–6.
27. Miller AE. Selective decline in cellular immune response to varicella-zoster in the elderly. Neurology **1980**; 30:582–7.
28. Berger R, Florent G, Just M. Decrease of the lymphoproliferative response to varicella-zoster virus antigen in the aged. Infect Immun **1981**; 32:24–27.
29. Burke BL, Steele RW, Beard OW, Wood JS, Cain TD, Marmer DJ. Immune response to varicella-zoster in the aged. Arch Intern Med **1982**; 142:291–3.
30. Hayward AR, Herberger M. Lymphocyte responses to varicella-zoster virus in the elderly. J Clin Immunol **1987**; 7:174–8.
31. Levin MJ, Murray M, Rotbart HA, Zerbe GO, White CJ, Hayward AR. Immune response of elderly individuals to a live attenuated varicella vaccine. J Infect Dis **1992**; 166:253–9.
32. Levin MJ, Smith JG, Kaufhold RM, et al. Decline in varicella-zoster virus (VZV)–specific cell-mediated immunity with increasing age and boosting with a high-dose VZV vaccine. J Infect Dis **2003**; 188:1336–44.
33. Takahashi M, Otsuka T, Okuno Y, Asano Y, Yazaki T. Live vaccine used

to prevent the spread of varicella in children in hospital. Lancet **1974**;2: 1288–90.
34. Asano Y, Nagai T, Miyata T, et al. Long-term protective immunity of recipients of the Oka strain of live varicella vaccine. Pediatrics **1985**; 75:667–71.
35. Weibel RE, Neff BJ, Kuter BJ, et al. Live attenuated varicella virus vaccine: efficacy trial in healthy children. N Engl J Med **1984**; 310: 1409–15.
36. Gershon AA, Steinberg SP, LaRussa P, Ferrara A, Hammerschlag M, Gelb L. Immunization of healthy adults with live-attenuated varicella vaccine. J Infect Dis **1988**; 158:132–7.
37. Takahashi M, Iketani T, Sasada K, et al. Immunization of the elderly and patients with collagen vascular diseases with live varicella vaccine and use of varicella skin antigen. J Infect Dis **1992**; 166:S58–62.
38. Levin MJ, Barber D, Goldblatt E, et al. Use of a live attenuated varicella vaccine to boost varicella-specific immune responses in seropositive people 55 years of age and older: duration of booster effect. J Infect Dis **1998**; 178:S109–12.
39. Trannoy E, Berger R, Hollander G, et al. Vaccination of immunocompetent elderly subjects with a live attenuated Oka strain of varicella zoster virus: a randomized, controlled, dose-response trial. Vaccine **2000**; 18:1700–6.
40. Redman RL, Nader S, Zerboni L, et al. Early reconstitution of immunity and decreased severity of herpes zoster in bone marrow transplant recipients immunized with inactivated varicella vaccine. J Infect Dis **1997**; 176:578–85.
41. Hata A, Asanuma H, Rinki M, et al. Use of an inactivated varicella vaccine in recipients of hematopoietic-cell transplants. N Engl J Med **2002**; 347:26–34.
42. Levin MJ, Hayward AR. The varicella vaccine: prevention of herpes zoster. Infect Dis Clin North Am **1996**; 10:657–75.
43. Levin, MJ. Use of varicella vaccines to prevent herpes zoster in older individuals. Arch Virol Suppl **2001**; (17):151–60.
44. Coplan PM, Schmader K, Nikas A, et al. Development of a measure of the burden of pain due to herpes zoster and postherpetic neuralgia for prevention trials: adaptation of the brief pain inventory. J Pain **2004**; 5:344–56.
45. Daut RL, Cleeland CS, Flanery RC, et al. Development of the Wisconsin brief pain questionnaire to assess pain in cancer and other diseases. Pain **1983**; 17:197–210.
46. Chang MN, Guess HA, Heyse JF. Reduction in burden of illness: a new efficacy measure for prevention trials. Stat Med **1994**; 13:1807–14.
47. Brisson M, Gay NJ, Edmunds WJ, Andrews N. Exposure to varicella boosts immunity to herpes-zoster: implications for mass vaccination against chickenpox. Vaccine **2002**; 20:2500–7.
48. Wagenpfeil S, Neiss A, Wutzler P. Effects of varicella vaccination on herpes zoster incidence. Clin Microbiol Infect **2004**; 10:954–60.