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A Vaccine to Prevent Herpes Zoster and Postherpetic Neuralgia in Older Adults

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ABSTRACT

BACKGROUND

The incidence and severity of herpes zoster and postherpetic neuralgia increase with age in association with a progressive decline in cell-mediated immunity to varicella–zoster virus (VZV). We tested the hypothesis that vaccination against VZV would decrease the incidence, severity, or both of herpes zoster and postherpetic neuralgia among older adults.

METHODS

We enrolled 38,546 adults 60 years of age or older in a randomized, double-blind, placebo-controlled trial of an investigational live attenuated Oka/Merck VZV vaccine ("zoster vaccine"). Herpes zoster was diagnosed according to clinical and laboratory criteria. The pain and discomfort associated with herpes zoster were measured repeatedly for six months. The primary end point was the burden of illness due to herpes zoster, a measure affected by the incidence, severity, and duration of the associated pain and discomfort. The secondary end point was the incidence of postherpetic neuralgia.

RESULTS

More than 95 percent of the subjects continued in the study to its completion, with a median of 3.12 years of surveillance for herpes zoster. A total of 957 confirmed cases of herpes zoster (315 among vaccine recipients and 642 among placebo recipients) and 107 cases of postherpetic neuralgia (27 among vaccine recipients and 80 among placebo recipients) were included in the efficacy analysis. The use of the zoster vaccine reduced the burden of illness due to herpes zoster by 61.1 percent ($P<0.001$), reduced the incidence of postherpetic neuralgia by 66.5 percent ($P<0.001$), and reduced the incidence of herpes zoster by 51.3 percent ($P<0.001$). Reactions at the injection site were more frequent among vaccine recipients but were generally mild.

CONCLUSIONS

The zoster vaccine markedly reduced morbidity from herpes zoster and postherpetic neuralgia among older adults.

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Herpes zoster, or shingles, is characterized by unilateral radicular pain and a vesicular rash that is generally limited to a single dermatome.[1,2] Herpes zoster results from reactivation of latent varicella–zoster virus (VZV) within the sensory ganglia.[3,4] The incidence and severity of herpes zoster increase with advancing age; more than half of all persons in whom herpes zoster develops are older than 60 years. Complications occur in almost 50 percent of older persons with herpes zoster.[3-5] The most frequent debilitating complication is postherpetic neuralgia, a neuropathic pain syndrome that persists or develops after the dermatomal rash has healed.[5-9] The frequency and severity of postherpetic neuralgia also increase with increasing age.[9-11] The pain and discomfort associated with herpes zoster can be prolonged and disabling, diminishing the patient's quality of life and ability to function to a degree comparable to that in diseases such as congestive heart failure, myocardial infarction, diabetes mellitus type 2, and major depression.[12] Antiviral therapy reduces the severity and duration of herpes zoster but does not prevent the development of postherpetic neuralgia.[2,11] Postherpetic neuralgia may persist for years and is often refractory to treatment.[13]

Forty years ago, Hope-Simpson proposed that immunity to VZV plays a pivotal role in the pathogenesis of herpes zoster,[3] and subsequent observations support the thesis that cell-mediated immunity to VZV is a major determinant of the risk and severity of herpes zoster.[3,7,11,14-17] Whereas levels of antibody to VZV remain relatively constant with increasing age, the increased incidence and severity of herpes zoster and postherpetic neuralgia among older adults are closely linked to a progressive age-related decline in cell-mediated immunity to VZV.[4-8,14-21] Recurrences of herpes zoster are uncommon among immunocompetent persons, presumably because an episode of herpes zoster boosts immunity to VZV, effectively "immunizing" against a subsequent episode.[3,4,7,8,22]

Previous studies have shown that VZV vaccines can elicit a significant increase in cell-mediated immunity to VZV in immunocompetent older adults[21-25] and reduce the incidence and severity of herpes zoster in recipients of bone marrow allografts.[26,27] These observations led us to hypothesize that immunization of older persons with a VZV vaccine would boost their cell-mediated immunity to VZV and thereby provide protection against herpes zoster and postherpetic neuralgia.[22] The Shingles Prevention Study (Department of Veterans Affairs [VA] Cooperative Study No. 403) was conducted to determine whether vaccination with a live attenuated VZV vaccine would decrease the incidence, severity, or both of herpes zoster and postherpetic neuralgia in adults 60 years of age or older.

METHODS

A detailed description of the methods used in this study is provided in the Supplementary Appendix (available with the full text of this article at www.nejm.org). A brief overview is presented here.

STUDY DESIGN

We conducted a randomized, placebo-controlled, double-blind clinical trial at 22 sites, in which adults 60 years of age or older received either VZV vaccine or placebo. The study was approved by a human rights committee of the VA Cooperative Studies Program (VACSP) and by the local institutional review boards at all study sites. An independent data and safety monitoring board reviewed the safety data and the interim results.

STUDY POPULATION

Eligible subjects had a history of varicella or had resided in the continental United States for at least 30 years. Immunocompromised persons and those unable to adhere to the study protocol were excluded. All subjects provided written informed consent.

INTERVENTION

Subjects received one subcutaneous injection of 0.5 ml of the investigational live attenuated Oka/Merck VZV vaccine ("zoster vaccine") or placebo. The estimated potency at vaccination of the 12 vaccine lots used in the study ranged from 18,700 to 60,000 plaque-forming units per dose. The median potency was 24,600 plaque-forming units, and more than 90 percent of vaccinated subjects received 32,300 plaque-forming units or less.

FOLLOW-UP

Active follow-up and ascertainment of cases of herpes zoster were ensured by an interactive automated telephone-response system, which subjects called monthly. If a subject's responses to a standardized set of questions suggested a possible case of herpes zoster, the subject was instructed to contact the local study site immediately, and a fax con-

taining the subject's response was sent to the site. Subjects who did not call the automated telephone-response system within a pre-established length of time were called by the automated telephone-response system. If this effort to reach the subject failed, the local study site was notified by fax to contact the subject directly. At the end of the study, subjects were asked to report any previously unreported episodes of herpes zoster.

SAFETY EVALUATION

All adverse events occurring within 42 days after vaccination were recorded. Thereafter, only serious adverse events were recorded if reported by the subject and considered by the study physician to be related to the vaccination. Deaths were identified on the basis of reports from family members and during follow-up of missed monthly calls to the automated telephone-response system.

Approximately 300 subjects at each of the study sites were enrolled in a substudy that more closely monitored adverse events. These subjects maintained a daily log of body temperature and a "report card" of symptoms related to the injection site and other clinical symptoms during the 42 days after vaccination. Thereafter, they were followed to identify all hospitalizations.

IDENTIFICATION AND EVALUATION OF SUSPECTED CASES OF HERPES ZOSTER

At enrollment, the subjects were educated with regard to the signs and symptoms of herpes zoster. Those who had a new rash or new unilateral pain were urged to contact their study site immediately. Study personnel attempted to evaluate all subjects with new rashes as soon as possible. Subjects with unilateral rashes and no alternative clinical diagnoses were classified as having "suspected cases of herpes zoster" and were followed according to the study protocol. The evaluating physician offered subjects with clinically diagnosed herpes zoster, without cost, the licensed antiviral drug famciclovir (Famvir, SmithKline Beecham and Novartis Pharmaceuticals), in accordance with the manufacturer's recommendations, and with standard-of-care treatment for pain. Pain management was not specified by the study protocol.

Herpes zoster–associated pain (including unpleasant sensations such as allodynia and pruritus, which are not always characterized as pain by persons with herpes zoster) was measured with the use of the Zoster Brief Pain Inventory, an assessment tool in the form of a questionnaire completed by the subject that was specifically designed to measure pain and discomfort in herpes zoster.[28] This questionnaire and others[29,30] were used to assess the effect of herpes zoster on the subjects' activities of daily living, quality of life, and general health status. Characteristics of the rash, associated complications, and medication use were also recorded. Evaluations based on responses to the questionnaires were repeated over a period of at least 182 days, according to a schedule specified by the study protocol. Digital photographs and specimens for laboratory diagnosis were obtained from subjects with suspected cases of herpes zoster.

CONFIRMATION OF CASES

Before unblinding, each suspected case of herpes zoster was classified as a confirmed case of herpes zoster or as not a confirmed case with the use of a hierarchical algorithm that incorporated the results of the polymerase-chain-reaction (PCR) assay performed at the central laboratory of the study, virus culture at the local virology laboratory, and the final clinical diagnosis of the study's clinical evaluation committee, consisting of five physicians with expertise in herpes zoster.

The PCR assay, designed to detect and discriminate among DNA from wild-type and vaccine strains of VZV and from herpes simplex virus (HSV), could detect approximately 13 copies of DNA from wild-type or the vaccine strain of VZV. The PCR assays included primers and a probe for the human beta-globin gene to verify the presence of cellular DNA in the specimens from the lesions.

If the PCR assay revealed VZV DNA, the suspected case of herpes zoster was classified as a confirmed case; if the assay was positive for beta-globin or HSV DNA and negative for VZV DNA, the case was classified as not a case of herpes zoster. If the specimen obtained for the assay was inadequate (i.e., was negative for both viral and beta-globin DNA) or was missing, the final diagnosis was determined by the isolation of VZV or HSV in the local virology laboratory. In the absence of a valid laboratory diagnosis, the case was classified on the basis of the clinical diagnosis by the clinical evaluation committee.

EFFICACY END POINTS

The primary end point was the burden of illness due to herpes zoster, a severity-by-duration measure of the total pain and discomfort associated with her-

pes zoster in the population of study subjects.[28,31,32] For each confirmed case of herpes zoster, responses to the "worst pain" question in the Zoster Brief Pain Inventory were used to calculate a herpes-zoster severity-of-illness score, defined as the area under the curve (AUC) of herpes-zoster pain plotted against time during the 182-day period after the onset of rash. Subjects in whom herpes zoster developed had severity-of-illness scores ranging from 0 to 1813. Increasing mean scores are highly correlated with a decrease in the health-related quality of life and in functional status among older adults.[28,33] A score of 0 was recorded for subjects in whom herpes zoster did not develop during the study period.

The "herpes-zoster burden-of-illness score" represented the average severity of illness among all subjects in the vaccine or placebo groups; it was calculated as the sum of the herpes-zoster severity-of-illness scores of all members of a group divided by the total number of subjects in the group. The secondary end point was the incidence of postherpetic neuralgia, defined as pain associated with herpes zoster that was rated as 3 or more on a scale ranging from 0 ("no pain") to 10 ("pain as bad as you can imagine"), persisting or appearing more than 90 days after the onset of rash. Scores lower than 3 were not associated with significant decrements in the quality of life or the ability to carry out activities of daily living and were therefore not considered to represent postherpetic neuralgia.[10,28]

STATISTICAL ANALYSIS

A data-analysis plan was completed before the data were unblinded for analysis.[31,34-38] The analysis was performed by the VACSP coordinating center (West Haven, Conn.), with review and approval by the executive committee of the study. Vaccine efficacy with respect to the burden of illness due to herpes zoster (VE_{BOI}) was defined as the relative reduction in the burden-of-illness score in the vaccine group as compared with that in the placebo group and calculated as 1−relative risk (i.e., 1−the herpes-zoster burden-of-illness score in the vaccine group divided by the herpes-zoster burden-of-illness score in the placebo group). The prespecified criteria for the success of the vaccine with respect to the burden of illness due to herpes zoster required a VE_{BOI} point estimate of 47 percent or more and a lower bound of the 95 percent confidence interval greater than 25 percent. A method of assessing the combined effect of disease incidence, severity, and duration, weighted for age group, was used.[31]

Vaccine efficacy with respect to the incidence of postherpetic neuralgia (VE_{PHN}) was defined as the relative reduction in the incidence of postherpetic neuralgia in the vaccine group as compared with that in the placebo group. The prespecified criteria for the success of the vaccine with respect to the incidence of postherpetic neuralgia required a VE_{PHN} point estimate of 62 percent or more and a lower bound of the 95 percent confidence interval greater than 25 percent. The VE_{PHN} was calculated with the use of a conditional exact method weighted for age group.[34-36] The VE_{PHN} was also calculated with the use of alternative definitions of postherpetic neuralgia as pain present for more than 30, 60, 120, and 182 days after the onset of rash caused by herpes zoster. Vaccine efficacy with respect to the incidence of herpes zoster (VE_{HZ}) was calculated similarly.

Efficacy analyses were performed with the use of a follow-up period that excluded the first 30 days after vaccination and excluded subjects who withdrew and those in whom a confirmed case of herpes zoster developed within the first 30 days after vaccination. The results were essentially unchanged when subjects in whom herpes zoster developed during the first 30 days were included. All reported P values are two-sided.

CONDUCT OF THE STUDY

The study was designed by the planning and executive committees of the Shingles Prevention Study Group, the members of which were selected for relevant expertise, with the support of a planning grant from the VACSP to the study chairs (details are provided in the Supplementary Appendix). Merck contributed to the planning process through two nonvoting members on these committees. The statistical methods for analyzing burden of illness were developed and published by Merck statisticians before the initiation of the study.[31] The study was initiated and implemented as a VA Cooperative Study in collaboration with the National Institute of Allergy and Infectious Diseases and Merck. Merck, the holder of the investigational new drug application, participated in the organization of oversight activities and monitored the progress of the study. The Covalent Group, an independent company, was hired by Merck to monitor case report forms and adherence to the study protocol and to report to Merck and the VACSP. The participating investigators and their staff gathered the data. An unblinded statistician at the VACSP coordinating center, who was not involved in the operation of the study, pre-

sented unblinded safety data to the data and safety monitoring board.

Management and consolidation of the data were performed by the VACSP coordinating center. Data-analysis programs were developed and tested by biostatisticians and programmers at the coordinating center and at Merck. The data were analyzed at the coordinating center. The executive committee reviewed and approved the data-analysis plan and all analyses of vaccine efficacy and safety and vouches for the study's results. The writing committee, all members of which were also members of the executive committee, wrote the manuscript and takes responsibility for it.

RESULTS

CHARACTERISTICS OF THE STUDY SUBJECTS

A total of 38,546 subjects were enrolled in the study between November 1998 and September 2001 (Fig. 1). The numbers enrolled at each study site ranged from 1167 to 2508. Follow-up was completed in April 2004. The demographic characteristics of the two study groups were similar (Table 1). The median age in both groups was 69 years; 6.6 percent of the vaccine recipients and 6.9 percent of the placebo recipients were 80 years of age or older. At enrollment, most of the subjects had no health-related limitations on their activities (51.3 percent) or mild health-related limitations (38.6 percent). More than 95 percent of the subjects were actively followed to the end of the study (Fig. 1) and completed a closeout interview. The mean duration of herpes zoster surveillance was 3.13 years (median, 3.12 years; range, 1 day to 4.90 years) with no difference in duration between the groups. Only 0.6 percent of the subjects withdrew from the study or were lost to follow-up; 4.1 percent died during the study.

CONFIRMED CASES FOR THE EFFICACY ANALYSES

More than 3500 rashes that developed in subjects in each treatment group were evaluated clinically but were not considered to be suspected cases of herpes zoster. A total of 1308 subjects with suspected herpes zoster were evaluated according to the protocol (Fig. 1). Among these subjects, 317 (156 in the vaccine group and 161 in the placebo group) were determined not to have herpes zoster. Of these 317 subjects, 49 had rashes that were caused by HSV (24 in the vaccine group and 25 in the placebo group). Closeout interviews did not identify any previously unreported cases of herpes zoster. Of the 1308 suspected cases of herpes zoster, the final diagnosis in 1156 cases (88.4 percent; 417 in the vaccine group and 739 in the placebo group) was based on the results of the PCR assay.

Of the 1308 suspected cases, 984 (75.2 percent) were determined to be confirmed cases. In accordance with the protocol, 24 cases were excluded from the efficacy analyses because they occurred within 30 days of vaccination (6 in the vaccine group and 18 in the placebo group) and 3 because they were a subject's second episode of herpes zoster (Fig. 1). The remaining 957 confirmed cases of herpes zoster (315 in the vaccine group and 642 in the placebo group) constituted the end points of the efficacy analyses. The results of PCR testing were positive for wild-type VZV DNA in more than 93 percent of the confirmed cases of herpes zoster in each study group (Fig. 1). Vaccine virus DNA was not detected in any subjects with suspected herpes zoster.

The rate of use of antiviral medication among subjects with confirmed cases of herpes zoster was similar in the two groups (87.3 percent in the vaccine group and 85.7 percent in the placebo group), as was the proportion in whom treatment was initiated within 72 hours of the onset of rash — in 64.1 percent in the vaccine group and 65.9 percent in the placebo group. The frequency of use of various medications to treat pain resulting from herpes zoster was similar in the two groups, and the average duration of the use of opioids and the average quantity of opioids used among subjects with herpes zoster were greater in the placebo group than in the vaccine group. Thus, differences in the use of pain medication did not inflate the estimates of VE_{BOI} or VE_{PHN}.

BURDEN OF ILLNESS DUE TO HERPES ZOSTER

The herpes-zoster burden-of-illness score was significantly reduced in the vaccine group as compared with the placebo group ($P<0.001$) (Table 2). Overall, VE_{BOI} was 61.1 percent (95 percent confidence interval, 51.1 to 69.1), a result that met the prespecified criteria for success. There were no significant differences in the VE_{BOI} when the results were stratified according to sex or age (Table 2).

INCIDENCE OF POSTHERPETIC NEURALGIA

There were 107 cases of postherpetic neuralgia, 27 in the vaccine group and 80 in the placebo group (0.46 case vs. 1.38 cases per 1000 person-years, respectively; $P<0.001$) (Table 3). Overall, the VE_{PHN}

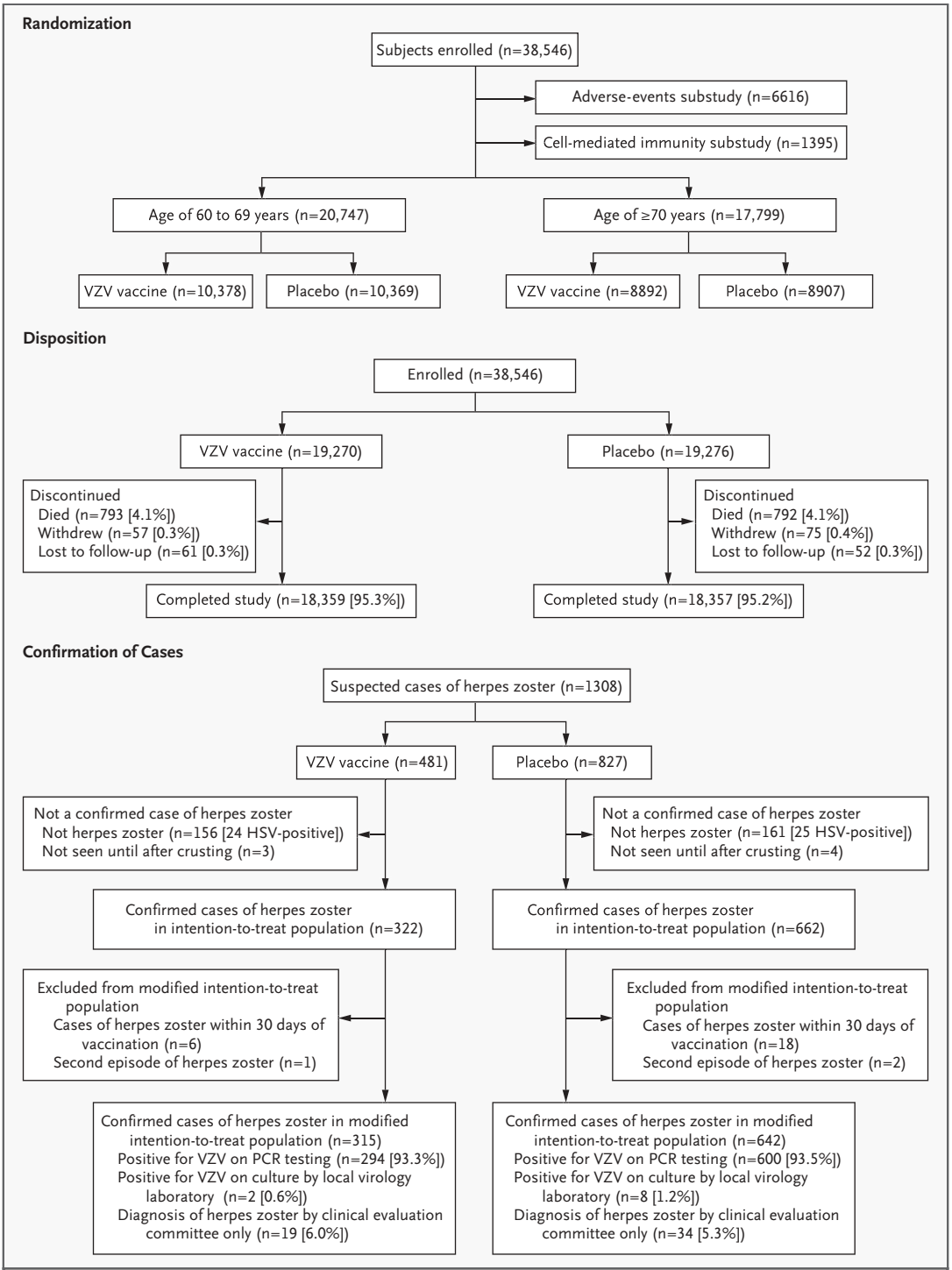

Figure 1. Diagram of the Study Design and Results.

The intention-to-treat population included all subjects who underwent randomization. Efficacy analyses were performed with the use of a follow-up interval that excluded the first 30 days after vaccination and the modified intention-to-treat population, which excluded subjects who withdrew or in whom a confirmed case of herpes zoster developed within the first 30 days after vaccination. For three subjects in whom more than one confirmed case of herpes zoster developed, only the first case was included in the modified intention-to-treat analyses. HSV denotes herpes simplex virus, and VZV varicella–zoster virus.

was 66.5 percent (95 percent confidence interval, 47.5 to 79.2), a result that met the prespecified criteria for success. There were no significant differences in the VE_{PHN} when the results were stratified according to sex or age (Table 3).

The VE_{PHN} did not change appreciably when postherpetic neuralgia was defined with the use of alternative cutoff times for the duration (persistence) of pain (Table 3). In a time-to-event analysis, the cumulative incidence of postherpetic neuralgia was significantly lower in the vaccine group than in the placebo group (P<0.001) (Fig. 2A).

INCIDENCE OF HERPES ZOSTER

The overall incidence of herpes zoster per 1000 person-years was significantly reduced by the zoster vaccine, from 11.12 per 1000 person-years in the placebo group to 5.42 per 1000 person-years in the vaccine group (P<0.001) (Table 2). The VE_{HZ} was 51.3 percent (95 percent confidence interval, 44.2 to 57.6). In a time-to-event analysis, the cumulative incidence of herpes zoster was significantly lower in the vaccine group than in the placebo group (P<0.001) (Fig. 2B). The VE_{HZ} was 37.6 percent among subjects 70 years of age or older and 63.9 percent among younger subjects (P<0.001). There was no difference in VE_{HZ} according to sex.

DURATION AND SEVERITY OF HERPES ZOSTER

The median duration of pain and discomfort among subjects with confirmed cases of herpes zoster was significantly shorter in the vaccine group than in the placebo group (21 days vs. 24 days, P=0.03). Similarly, the mean herpes-zoster severity-of-illness score (AUC) among subjects with confirmed cases of herpes zoster was significantly lower in the vaccine group than in the placebo group (141.2 vs. 180.5, P=0.008). For almost every level of the severity-of-illness score, there were fewer cases of herpes zoster in the vaccine group than in the placebo group. The effect of the zoster vaccine on the severity of illness was greater among older subjects; thus, the VE_{BOI}, the primary end point of the study, was maintained at 55.4 percent.

VACCINE SAFETY IN THE TOTAL STUDY POPULATION

Over the entire study period, the numbers and percentages of deaths were similar in both study groups (Table 4). During the first 42 days after vaccination, the number and types of serious adverse events were similar in the two groups (Table 4), as

Table 1. Baseline Characteristics of the Study Participants.*

Characteristic	Vaccine Group (N=19,270)	Placebo Group (N=19,276)
Demographic		
Age — no. (%)		
60–69 yr	10,378 (53.9)	10,369 (53.8)†
≥70 yr	8,892 (46.1)	8,907 (46.2)
Sex — no. (%)		
Male	11,403 (59.2)	11,357 (58.9)
Female	7,867 (40.8)	7,919 (41.1)
Race — no. (%)‡		
White	18,393 (95.4)	18,381 (95.4)
Black	395 (2.0)	420 (2.2)
Hispanic	265 (1.4)	248 (1.3)
Other or unknown	217 (1.1)	227 (1.2)
General health status		
EuroQol thermometer score§		
Mean ±SD	86.4±11.7	86.3±11.6
Median	90	90
Interquartile range	80–95	80–95
Difficulty walking — no. (%)		
No	11,514 (59.8)	11,402 (59.2)
Rarely	2,464 (12.8)	2,536 (13.2)
Sometimes	3,380 (17.5)	3,475 (18.0)
Often	1,109 (5.8)	1,033 (5.4)
All the time	801 (4.2)	826 (4.3)
Difficulty going places — no. (%)		
No	15,303 (79.4)	15,272 (79.2)
Rarely	2,084 (10.8)	2,079 (10.8)
Sometimes	1,394 (7.2)	1,433 (7.4)
Often	313 (1.6)	327 (1.7)
All the time	174 (0.9)	161 (0.8)
Health-related limitations on activities — no. (%)		
No	9,924 (51.5)	9,862 (51.2)
Mild	7,440 (38.6)	7,423 (38.5)
Moderate	1,637 (8.5)	1,714 (8.9)
Severe	266 (1.4)	273 (1.4)

* Not all subjects responded to every question in the questionnaires. Percentages are rounded.
† One subject was 59 years of age.
‡ Race was self-reported on a questionnaire administered at enrollment.
§ The EuroQol thermometer is a visual-analogue scale for patients to use to rate their overall status from 0 (worst imaginable health) to 100 (best imaginable health). The thermometer is included in the EuroQol questionnaire regarding the quality of life, on which patients graded their general health status in the categories shown.

Table 2. Effect of Zoster Vaccine on the Burden of Illness in Herpes Zoster in the Modified Intention-to-Treat Population.*

Group of Subjects	Vaccine Group			Placebo Group			VE_{BOI} (95% CI)§
	No. of Confirmed Cases/No. of Subjects	BOI Score†	Incidence per 1000 Person-Yr‡	No. of Confirmed Cases/No. of Subjects	BOI Score†	Incidence per 1000 Person-Yr‡	
							%
All subjects	315/19,254	2.21	5.42	642/19,247	5.68	11.12	61.1 (51.1–69.1)
Age							
60–69 yr	122/10,370	1.50	3.90	334/10,356	4.33	10.79	65.5 (51.5–75.5)
≥70 yr	193/8884	3.47	7.18	308/8891	7.78	11.50	55.4 (39.9–66.9)
Sex							
Male	181/11,390	2.09	5.30	361/11,337	5.81	10.65	64.0 (51.4–73.4)
Female	134/7864	2.34	5.58	281/7910	5.47	11.79	57.3 (39.6–69.8)

* Efficacy analyses were performed with the use of a follow-up interval that excluded the first 30 days after vaccination and in a modified intention-to-treat population, which excluded subjects who either withdrew from the study or in whom a confirmed case of herpes zoster developed within the first 30 days after vaccination. Of three subjects in whom more than one case of herpes zoster developed, only the first case was included. VE_{BOI} denotes vaccine efficacy for the burden of illness due to herpes zoster (BOI), and CI confidence interval.

† For the total population and the subgroups stratified according to sex, the BOI score in each treatment group (vaccine or placebo) was the weighted average of the observed BOI stratified according to age, with weights proportional to the total number of subjects within each age group; subjects in whom herpes zoster did not develop were assigned a score of 0 for severity of illness due to herpes zoster on the basis of the Zoster Brief Pain Inventory, a questionnaire developed for the Shingles Prevention Study.

‡ For the total population and for subgroups stratified according to sex, the incidence of herpes zoster in each treatment group was the weighted average of the observed incidence of herpes zoster stratified according to age group, with weights proportional to the total number of person-years of follow-up in each age group.

§ VE_{BOI} for all subjects was the protocol-specified primary end point.

was the distribution of serious adverse events according to body system (data not shown). During this period, varicella-like rashes at the injection site occurred more frequently among those in the vaccine group than among those in the placebo group, but varicella-like rashes at other sites occurred at similar rates in the two groups (Table 4). There were 7 confirmed cases of herpes zoster in the vaccine group and 24 in the placebo group during the first 42 days after vaccination.

Five subjects had serious adverse events that were assessed by site investigators as possibly vaccine-related. Two subjects had received vaccine: a 64-year-old woman who had an exacerbation of asthma two days after receiving the vaccination, and an 80-year-old man in whom symptoms of polymyalgia rheumatica developed on day 3. The remaining three subjects, all men, who had serious adverse events had received placebo: the first subject was 65 years of age and had an anaphylactoid reaction 90 minutes after receiving the vaccination (and 30 minutes after eating peanuts); the second was 69 years of age and received a diagnosis of polymyalgia rheumatica on day 15; and the third was 78 years of age and received a diagnosis of Goodpasture's syndrome on day 52.

ADVERSE-EVENTS SUBSTUDY

In the adverse-events substudy, a significantly greater number of subjects in the vaccine group had one or more adverse events than in the placebo group, reflecting a greater frequency of adverse events at the injection site among subjects in the vaccine group (Table 4). In the vaccine group, the most frequent adverse events at the injection site were erythema (in 35.8 percent of the vaccine group), pain or tenderness (in 34.5 percent), swelling (in 26.2 percent), and pruritus (in 7.1 percent). No other adverse event at the injection site was observed in more than 2 percent of the vaccine recipients. Overall, the proportion of subjects with one or more systemic adverse events was similar in the two groups;

Table 3. Effect of Zoster Vaccine on the Incidence of Postherpetic Neuralgia in the Modified Intention-to-Treat Population.*

Variable	Vaccine Group			Placebo Group			VE_{PHN} (95% CI)
	No. of Confirmed Cases of Herpes Zoster with PHN	No. of Subjects	Incidence per 1000 Person-Yr†	No. of Confirmed Cases of Herpes Zoster with PHN	No. of Subjects	Incidence per 1000 Person-Yr†	%
All subjects	27	19,254	0.46	80	19,247	1.38	66.5 (47.5–79.2)‡
Age							
60–69 yr	8	10,370	0.26	23	10,356	0.74	65.7 (20.4–86.7)
≥70 yr	19	8,884	0.71	57	8,891	2.13	66.8 (43.3–81.3)
Sex							
Male	19	11,390	0.56	51	11,337	1.50	62.8 (35.9–79.3)
Female	8	7,864	0.33	29	7,910	1.22	72.6 (38.6–89.2)
Persistence of PHN among all subjects§							
30 days	81		1.39	196		3.39	58.9 (46.6–68.7)
60 days	45		0.77	113		1.96	60.4 (43.6–72.6)
90 days	27		0.46	80		1.38	66.5 (47.5–79.2)‡
120 days	17		0.29	54		0.93	68.7 (45.2–83.0)
182 days	9		0.16	33		0.57	72.9 (42.1–88.6)

* For the secondary end point, postherpetic neuralgia (PHN) was defined as the pain and discomfort associated with herpes zoster rated as 3 or more, on a scale ranging from 0 (no pain) to 10 (pain as bad as you can imagine), persisting or appearing more than 90 days after the onset of herpes zoster rash. Efficacy analyses were performed with the use of a follow-up interval that excluded the first 30 days after vaccination and the modified intention-to-treat population, which excluded subjects who withdrew or in whom a confirmed case of herpes zoster developed within the first 30 days after vaccination. Of three subjects in whom more than one confirmed case of herpes zoster developed, only the first case was included. VE_{PHN} denotes vaccine efficacy for the incidence of PHN, and CI confidence interval.

† For the total population and the subgroups stratified according to sex, the incidence of PHN in each treatment group (vaccine or placebo) was the weighted average of the observed incidence of PHN stratified according to age group, with weights proportional to the total number of person-years of follow-up in each age group.

‡ VE_{PHN} for all subjects was the protocol-specified secondary end point.

§ PHN was defined as the pain and discomfort associated with herpes zoster that was rated as 3 or more persisting or appearing more than 30, 60, 90, 120, and 182 days after the onset of herpes zoster rash.

however, systemic adverse events assessed as vaccine-related occurred more frequently among vaccine recipients (Table 4).

In the substudy, during the 42 days after vaccination, significantly more subjects in the vaccine group had serious adverse events than in the placebo group (1.9 percent vs. 1.3 percent, respectively; P=0.03); there were no significant differences in the distribution of serious adverse events according to body system or type of event (data not shown). A post hoc, subject-by-subject review of serious adverse events conducted by the writing committee revealed no clinically meaningful differences between the groups in the pathophysiology, nature, timing, intensity, or outcome of these events.

The number of subjects who had one or more hospitalizations was similar in the two groups. No hospitalization among subjects in either group was considered to be related to the vaccine.

DISCUSSION

The pain and discomfort of herpes zoster and postherpetic neuralgia cause substantial morbidity among older adults.[9-12,15,28] Although herpes zoster is not a reportable disease, we estimate that 1 million or more cases occur each year in the United States, a number that is likely to increase as the population ages. Thus, a means of prevention would offer important medical and economic benefits.

The zoster vaccine reduced the burden of illness

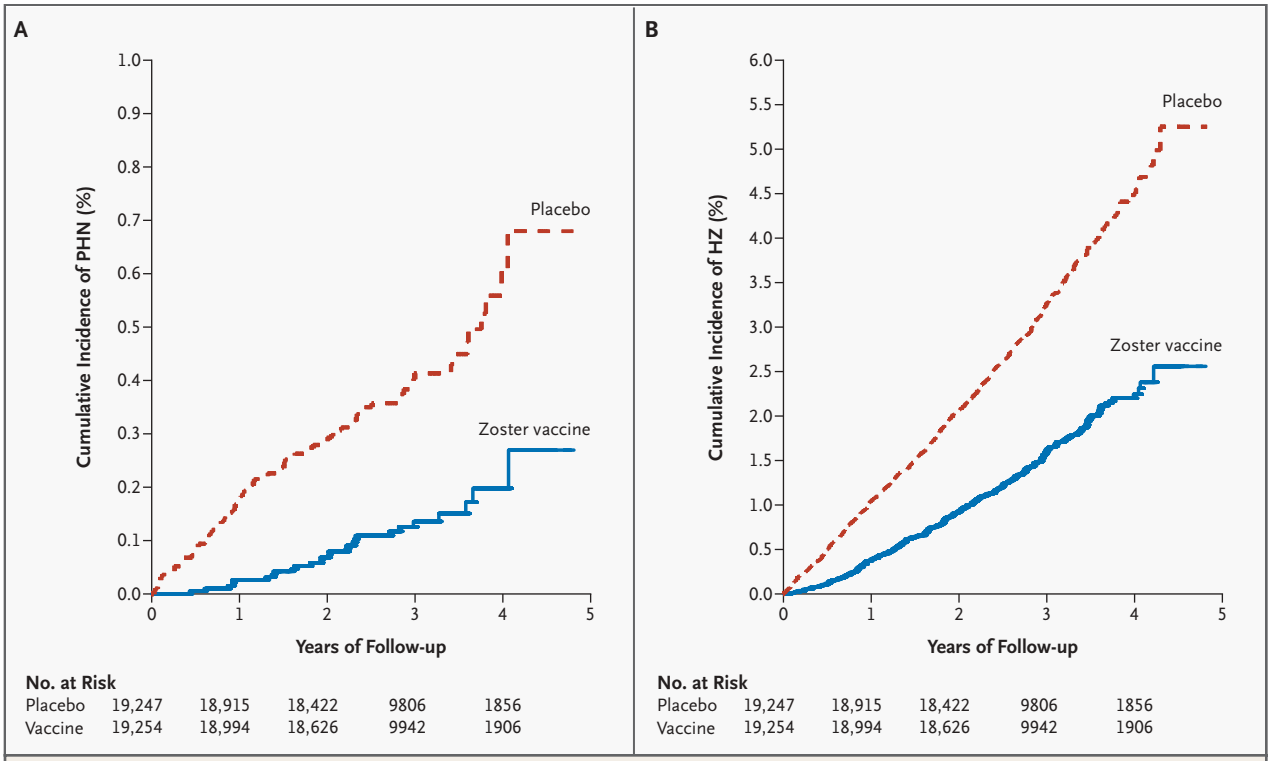

Figure 2. Kaplan–Meier Estimates of the Effect of Zoster Vaccine on the Cumulative Incidence of Postherpetic Neuralgia (Panel A) and Herpes Zoster (Panel B) in the Modified Intention-to-Treat Population.

Incidence rates of postherpetic neuralgia (PHN) and herpes zoster (HZ) were significantly lower in the vaccine group than in the placebo group ($P<0.001$, by a stratified log-rank test that pooled the results of the log-rank test from the two age groups). Cumulative incidence, expressed as a percentage of the subjects at risk, is the probability of the development of the disease during the period from 30 days after vaccination to the follow-up time.

due to herpes zoster among people 60 years of age or older by 61.1 percent and reduced the incidence of postherpetic neuralgia by 66.5 percent. Significant efficacy with respect to the incidence of postherpetic neuralgia was demonstrated, regardless of how postherpetic neuralgia was defined, with a trend toward greater efficacy for postherpetic neuralgia of longer duration. The vaccine also showed significant efficacy for these end points even when the results were stratified according to age and sex. Zoster vaccine also reduced the overall incidence of herpes zoster by 51.3 percent and significantly reduced the pain and discomfort among subjects in whom herpes zoster developed. Although the effect of zoster vaccine on the incidence of herpes zoster was less among older subjects than among younger subjects, the effect of the vaccine on the severity of illness was greater among older subjects, so that the VE_{BOI}, the primary end point of the study, was maintained at 55.4 percent.

We believe that the observed efficacy of the zoster vaccine reflects its ability to boost immunity to VZV in vaccinated subjects — an issue that will require further study. The investigational zoster vaccine had low rates of serious adverse events, systemic adverse events, hospitalization, and death. Results were similar in the two study groups, and local reactions at the vaccination site were generally mild. The greater number of early cases of herpes zoster in the placebo group, as compared with the vaccine group, and the fact that no vaccine virus DNA was detected, indicate that the vaccine did not cause or induce herpes zoster.

The minimum potency of the zoster vaccine administered to subjects in the study was at least 14 times greater than the minimum potency of Varivax (Merck), the vaccine currently licensed to prevent varicella. A preliminary study indicated that potencies of this magnitude are required to elicit a significant increase in the cell-mediated immunity to

Table 4. Adverse Events among All Subjects and among Those in the Adverse-Events Substudy.*

Event	Vaccine Group	Placebo Group	Difference in Risk (95% CI)
			%
All subjects			
No. of subjects	19,270	19,276	
Day of vaccination to end of study	*no. (%)*		
Death	793 (4.1)	795 (4.1)	0.01 (–1.2 to 1.2)†
Death according to age group			
60–69 yr	218 (2.1)	246 (2.4)	–0.80 (–2.0 to 0.4)†
≥70 yr	575 (6.5)	549 (6.2)	0.95 (–1.2 to 3.1)†
Vaccine-related serious adverse event‡	2 (<0.1)	3 (<0.1)	NC
Day of vaccination to day 42			
Death	14 (0.1)	16 (0.1)	–0.01 (–0.1 to 0.1)
One or more serious adverse events	255 (1.4)	254 (1.4)	0.01 (–0.2 to 0.3)
Varicella-like rash at injection site	20 (0.1)	7 (0.04)	0.07 (0.02 to 0.13)§
Varicella-like rash not at injection site	18 (0.1)	14 (0.1)	0.02 (–0.04 to 0.09)
Herpes-zoster–like rash	17 (0.1)	36 (0.2)	–0.10 (–0.18 to –0.03)§
Rash unrelated to herpes zoster	595 (3.2)	620 (3.3)	–0.13 (–0.49 to 0.23)
Confirmed case of herpes zoster	7 (<0.1)	24 (0.1)	–0.09 (–0.16 to –0.03)§
Subjects in the adverse event substudy			
No. of subjects	3345	3271	
Day of vaccination to end of study	*no. (%)*		
Subjects hospitalized	1137 (34.0)	1115 (34.1)	0.1 (–8.8 to 9.0)†
Hospitalization related to herpes zoster	5 (0.2)	6 (0.2)	–0.1 (–0.7 to 0.5)†
Day of vaccination to day 42			
One or more serious adverse events	64 (1.9)	41 (1.3)	0.7 (0.1 to 1.3)§
One or more adverse events	1929 (58.1)	1117 (34.4)	23.7 (21.3 to 26.0)§
One or more systemic adverse events	820 (24.7)	768 (23.6)	1.0 (–1.0 to 3.1)
One or more vaccine-related systemic adverse events‡	209 (6.3)	160 (4.9)	1.4 (0.3 to 2.5)§
Documented temperature 38.3°C or higher	27 (0.8)	27 (0.9)	0.0 (–0.5 to 0.4)
Self-reports of feeling abnormal temperature¶	231 (7.2)	190 (6.0)	1.2 (0.0 to 2.4)
One or more adverse events at injection site‖	1604 (48.3)	539 (16.6)	31.7 (28.3 to 32.6)§
Erythema	1188 (35.8)	227 (7.0)	28.8 (26.9 to 30.6)§
Pain or tenderness	1147 (34.5)	278 (8.5)	26.0 (24.1 to 27.9)§
Swelling	871 (26.2)	147 (4.5)	21.7 (20.1 to 23.4)§
Pruritus	237 (7.1)	33 (1.0)	6.1 (5.2 to 7.1)§
Warmth	57 (1.7)	11 (0.3)	1.4 (0.9 to 1.9)§
Hematoma	53 (1.6)	46 (1.4)	0.2 (–0.4 to 0.8)
Rash	10 (0.3)	3 (0.1)	0.2 (0.0 to 0.5)

* The rates of death and of hospitalization are percentages of subjects in each treatment group. Otherwise, percentages are rates weighted in proportion to the number of subjects with safety follow-up in each age group. NC denotes not calculated. Three subjects who had withdrawn from the study because of worsening health and subsequently died were included in the safety analysis.

† The difference in risk (vaccine group–placebo group) and the 95 percent confidence intervals for deaths and hospitalizations are based on the rates per 1000 subject-years of follow-up to account for differential follow-up among the study participants as a result of staggered enrollment. Otherwise, the differences in risk and 95 percent confidence intervals are based on an asymptotic method for the difference of two binomial proportions where the proportions are weighted according to the number of subjects with safety follow-up in each age group. Negative values for the difference in risk result when the rate in the placebo group is larger than that in the vaccine group.

‡ Events classified as possibly related to vaccination were assessed by a blinded investigator at each site.

§ $P<0.05$ for the comparison with the placebo group.

¶ A temperature of 38.3°C or higher was not documented.

‖ None of the adverse events related to the injection site were considered to be serious adverse events.

VZV among older adults — hence, the need to formulate a high-potency vaccine for this study. We know of no data to suggest that the licensed varicella vaccine would be efficacious in protecting older adults from herpes zoster or postherpetic neuralgia. Thus, we do not recommend the use of the current varicella vaccine in an attempt to protect against herpes zoster and postherpetic neuralgia. The results of our study show that vaccination of immunocompetent persons 60 years of age and older with live attenuated zoster vaccine (Oka/Merck) markedly decreases the morbidity associated with herpes zoster and the incidence of postherpetic neuralgia.

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This article is dedicated to the memory of the late Edgar Hope-Simpson, whose seminal observations and prescient hypotheses on herpes zoster provided our inspiration and rationale, and to the late John Franklin Enders, who taught us what really matters.

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CLINICAL TRIAL REGISTRATION

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