Long-Term Persistence of Zoster Vaccine Efficacy

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Running Title: Long-Term Persistence of Zoster Vaccine Efficacy

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Summary: The Long-Term Persistence Substudy (LTPS) of the Shingles Prevention Study (SPS) assessed persistence of zoster vaccine efficacy (VE) in a cohort of zoster vaccine recipients followed from 5 to 11 years post-vaccination. VE was lower in the LTPS than in SPS and the Short-Term Persistence Substudy, and was no longer statistically significant beyond 7 years post-vaccination.

Abstract

Background

The Shingles Prevention Study (VA Cooperative Study #403, SPS) demonstrated efficacy of zoster vaccine through four years post-vaccination (1,2). A Short-Term Persistence Substudy (STPS) conducted in a subpopulation of SPS participants during a period from 3.8 to 7.8 years post-vaccination demonstrated that zoster vaccine efficacy persisted for at least 5 years after vaccination. A Long-Term Persistence Substudy (LTPS) was undertaken to assess vaccine efficacy in a cohort of zoster vaccine recipients during the period from 5 to 10 years post-vaccination.

Methods

Surveillance, procedures for case determination, and follow-up were analogous to those employed in the SPS and STPS. Since most SPS placebo recipients received zoster vaccine prior to initiation of the LTPS, there was no longer a cohort of placebo recipients who could serve as an unvaccinated control group. Instead, placebo results from the SPS and STPS were used to calculate historical controls that served as the reference placebo group for the LTPS. The study objectives were to determine the duration of vaccine efficacy for the HZ burden of illness, the incidence of postherpetic neuralgia (PHN), and the incidence of herpes zoster (HZ). These outcomes were assessed in the LTPS population for each year from years 7 to 11 post-vaccination.

Results

The LTPS enrolled 6867 participants who had received zoster vaccine in the SPS. In the LTPS, compared with the SPS, vaccine efficacy decreased from 61.1% to 37.3% for the HZ burden of illness; from 66.5% to 35.4% for the incidence of PHN; and from 51.3% to 21.1% for the

incidence of HZ. Analysis of vaccine efficacy for all three outcome measures in each year post-vaccination showed declining efficacy from years seven through 11. The composite outcome of vaccine efficacy for the HZ burden of illness and the incidence of PHN was significantly greater than zero through year 10 post-vaccination, whereas vaccine efficacy for the incidence of HZ was significantly greater than zero only through year eight. The smaller study cohort in the LTPS and the use of historical controls introduces additional variability and potential bias into these results, but they were supported by sensitivity analyses.

Conclusions

Zoster vaccine efficacy for each study outcome decreased, but persisted, in the LTPS population. Vaccine efficacy for the HZ burden of illness and the incidence of PHN appeared to persist into year ten following vaccination, whereas vaccine efficacy for the incidence of HZ appeared to persist only through year eight.

Background

Herpes zoster (HZ) results from the reactivation, multiplication and spread of varicella-zoster virus (VZV) that remains latent in sensory neurons following earlier primary VZV infection (i.e., varicella or chickenpox) (1). VA Cooperative Study #403: The Shingles Prevention Study (SPS) was a randomized, double-blind, placebo-controlled efficacy trial of live attenuated Oka/Merck herpes zoster vaccine (zoster vaccine) in 38,546 adults ≥60 years of age. The SPS demonstrated that zoster vaccine reduced the HZ pain and discomfort burden of illness (BOI) by 61.1% (95% CI 51.1, 69.1), the incidence of postherpetic neuralgia (PHN) by 66.5% (95% CI 47.5, 79.2), and the incidence of HZ by 51.3% (95% CI, 44.2, 57.6) during a mean period of follow-up of 3.13 years. Vaccine efficacy for all three study endpoints persisted through four years post-vaccination (2, 3). Details of the SPS design, the study endpoints, and the primary study results have been previously published (2, 3). After completion of the SPS, follow-up for the persistence of zoster vaccine efficacy for a period ranging from 3.3 to 7.8 years post-vaccination was carried out in a cohort of 14,270 SPS participants from 12 of the 22 original study sites who were re-enrolled into a Short-Term Persistence Substudy (STPS) (4). In the STPS, zoster vaccine reduced the HZ burden of illness by 50.1% (95% CI 14.1, 71.0), the incidence of PHN by 60.1 (95% CI -9.8, 86.7%), and the incidence of HZ by 39.6% (95% CI, 18.2, 55.5) (4). Combining the results of the SPS and STPS, there was evidence of persistence of vaccine efficacy through year five after vaccination, but persistence was uncertain after that point (4). The Long-Term Persistence Substudy (LTPS) was undertaken to follow a cohort of vaccine recipients from the SPS for a period of five to ten years after vaccination to further assess the duration of zoster vaccine efficacy for the HZ pain and discomfort Burden of Illness (BOI), the incidence of PHN, and the incidence of HZ.

Patients and Methods:

Study design and timeline. The design and results of the SPS and STPS have been previously published (2-4). In March 2005, SPS placebo recipients who could still be contacted received zoster vaccine per SPS protocol (4, 5). Consequently, there was no longer a cohort of SPS placebo recipients who could serve as an unvaccinated control group. Re-enrollment into the non-randomized, open label, multicenter LTPS took place from March 9, 2006 to June 6, 2007. Follow-up then continued through June 2010, when closeout calls to study participants began. Surveillance for suspected cases of HZ ended on December 30, 2010 with closeout of the last subject. Follow-up of the last suspected case of HZ was completed on February 22, 2011.

Study population and sites. Participation in the LTPS was limited to SPS vaccine recipients at the 12 SPS sites that participated in the STPS. A telephone consent procedure to re-enroll subjects into the Long-Term Persistence Substudy was approved by the VA Cooperative Studies Program (CSP), the CSP Coordinating Center Human Rights Committee, and local institutional review boards. Inclusion and exclusion criteria were the same as in the SPS, except that immunocompromised participants were not excluded and only subjects who received zoster vaccine on SPS enrollment were included. Subjects with a prior diagnosis of HZ were not eligible. Planned study accrual was 7500 participants.

Follow-up. Active follow-up with surveillance for incident cases of HZ was the same as in the SPS and STPS. Participants completed a monthly rash screening questionnaire through an automated telephone response system (ATRS) and, when the ATRS interaction was not successful, site personnel called participants to determine if a new rash had occurred that might

have represented HZ, and to maintain and document a high level of retention in the study. Subjects were instructed to contact their study site immediately to report and arrange for evaluation of any rash or symptoms suggestive of HZ. As in the SPS, the threshold for evaluating suspected cases of HZ was set very low, to ensure evaluation of any mild, atypical, or vaccine-modified cases of HZ.

HZ case determination and endpoint measurements. Methods for evaluating suspected cases of HZ, including diagnosis, management, and measurement of HZ-associated pain and/or discomfort, were the same as those employed in the SPS. Subjects with suspected HZ were seen as soon as possible after rash onset; written consent was obtained to collect clinical follow-up data and diagnostic specimens from skin lesions for central polymerase chain reaction (PCR) analysis (6), and subjects were given famciclovir, if indicated. Local virus culture results were not recorded, but could be submitted with adjudication information. The Initial Zoster Impact Questionnaire (IZIQ) and Zoster Brief Pain Inventory (ZBPI) were used to record subject-reported pain and/or discomfort associated with HZ (2-4, 7, 8). These responses were used to determine the HZ Severity of Illness Score and the presence or absence of clinically significant PHN (defined as a ZBPI worst pain score of $\geq$3 on a 0-10 scale persisting or appearing >90 days after HZ rash onset) (2-4, 7, 8). The HZ severity-of-illness score (i.e., the burden of illness) for each case of HZ was defined as the area under the curve (AUC) of the ZBPI worst pain and/or discomfort severity plotted against time during the 182-day period after HZ rash onset (2, 3). Subjects with suspected HZ were evaluated as soon as possible after HZ rash onset, during the first week after rash onset if the rash was still evolving, then on days 8, 31, 61, 91, 121, 151 and 183, or as soon as possible thereafter. This evaluation included assessment of the rash, as well as HZ pain and/or discomfort. Frequency of follow-up was less frequent after week 4 compared to

the SPS, (monthly instead of weekly) (3). As in the SPS, evaluable cases of HZ were determined using a hierarchical algorithm based on central laboratory PCR assay results, local virus culture results, and results of clinical adjudication by the Clinical Evaluation Committee (CEC) (6). In contrast to the SPS, in which every suspected case of HZ was evaluated by the CEC, CEC adjudication was only used to determine the diagnosis when the specimen for PCR diagnosis was missing or inadequate.

The HZ burden of illness was a composite measure reflecting the incidence of HZ and the severity and duration of HZ pain and/or discomfort in a population of subjects. It was defined as the sum of the HZ severity-of-illness scores of all of the evaluable cases of HZ in the group (e.g., the 60-69 year old zoster vaccine recipients). Subjects who did not develop HZ were assigned an HZ severity-of-illness score of zero (2).

Statistical methods. The definition of the HZ burden of illness, as well as methods for calculating vaccine efficacy for study outcomes, have been previously published (2-4, 8, 9). The analysis of the incidence of HZ and PHN assumed a Poisson distribution for events and used a conditional exact method for calculating rates (10, 11, 12). Data management and statistical programming were performed using SAS programming language (13) with exact confidence limits calculated using StatXact (14). Vaccine efficacy for the HZ burden of illness and for the incidence of HZ and PHN were calculated for the entire LTPS period (primary analysis). Since there was no placebo control group, the incidence and burden of illness outcomes for the reference placebo population were estimated using historical control methodology and results from the placebo group in the SPS and STPS (16).

Three age-year adjusted models were employed to determine historical controls that varied with respect to the degree of inclusion of results from SPS and STPS and in incorporating a calendar-

time effect (16). Adjustment for age was included for the association of incidence of HZ with increasing age, and the experience of age-related effects on vaccine efficacy. In addition, in the analysis of the SPS and STPS, it was noted that the age-specific incidence of HZ in the placebo group increased over calendar time (i.e., a "calendar effect"), but there was no comparable increase in the incidence of PHN or in the HZ Severity-of-Illness Scores. Therefore, the calendar effect was included in the two models used in the determination of historical controls. The three approaches defined in the LTPS statistical analysis plan were: 1) conservative (sensitivity analysis #1): include only data from SPS with no calendar-time effect; 2) intermediate (primary analysis): include data from SPS with a calendar-year effect; and 3) contemporary (sensitivity analysis #3) include data from SPS and recently completed STPS with a calendar-year effect. Analyses were stratified by age at randomization in the SPS into two pre-specified age groups: 60-69 years of age, and 70 years of age or older. Supportive analyses to assess the change in vaccine efficacy over each year of follow-up in the SPS, STPS, and LTPS were also completed for the three study outcomes. The incidence of HZ within a specific year post-vaccination was calculated by dividing the number of cases of HZ occurring within that year by the number of subject-years of follow-up for subjects in that year, then calculating vaccine efficacy as 1 – (incidence of $HZ_{Vaccine}$/incidence of $HZ_{Historical\ Control}$). Vaccine efficacy for the incidence of PHN and the HZ burden of illness were calculated similarly. For the analyses by year post-vaccination, the SPS and STPS populations were pooled by adding the number of HZ cases and the number of person-years of follow-up from the two studies for each year after vaccination for years one to six, with methods published previously (4). For years seven and eight, the LTPS and STPS results were pooled. Only LTPS results existed for the analyses of years nine to eleven

post-vaccination. Results were presented as point estimates of event outcomes and as vaccine efficacy with 95 percent confidence intervals.

Objectives

The objectives of this study were to estimate the long-term vaccine efficacy of zoster vaccine in adults >60 years of age on the: 1) HZ pain burden of illness (BOI); 2) incidence of PHN, and 3) incidence of HZ.

Results

Study population. From March 2006 to April 2007, 7625 subjects were screened and 6867 (90%) were enrolled into the LTPS (Table 1; Figure 1). The majority of subjects (6546) came from re-enrollment of STPS subjects, but 321 were vaccine recipients who had not enrolled in the STPS. The main reasons for subjects not enrolling (n=758) were: subjects declined participation (n=433, 57%); were considered unlikely to adhere to the protocol (n=37, 4.9%); history of HZ (n=99, 13%). Of the 6867 subjects, 56.3% were male; age ranged from 64 to 95 (median, 74) years; 20.8% were >80 years of age; 97.8% were Caucasian. On average, subjects were six years older when they enrolled in the LTPS (mean, 74.5 years; SD= 5.8 years) than when they were randomized in the SPS (mean, 68.3 years). Enrolled participants were, on average, younger than the subjects who were screened but did not enroll in the LTPS (mean age, 68.3 versus 69.6 years, respectively). Of this cohort, 88% (6043/6867) completed follow-up per study protocol. Reasons for discontinuation included death (5.8%), withdrawal from the study (5.6%), and lost to follow-up (0.6%).

Surveillance and follow-up of HZ cases. LTPS participants accrued 25,250 subject-years of follow-up during the 58 months of the study. Mean follow-up time (± standard deviation) was 3.74 ± 0.0.75 years. At study end, 6043 (88%) of the 6867 enrolled subjects completed closeout

interviews, 399 (5.8%) died during the study, 382 (5.6%) withdrew, and 42 (0.6%) were lost to follow-up (Figure 1). Over the 58 months of surveillance in the LTPS, participants completed more than 90% of scheduled monthly contacts through the ATRS, and another 8.1% of monthly contacts were completed by telephone calls initiated by LTPS site personnel.

A total of 978 subjects with rashes and 13 subjects with unilateral pain/discomfort without rash were evaluated as suspected cases of HZ during the 58 months of the study. Of these, 347 (35.0%) were given a provisional diagnosis of HZ. Diagnostic specimens for central PCR assay were collected from 326 (94%) of these suspected cases of HZ; PCR assay results were obtained for 317 (91%), and CEC adjudication was completed for 30 (9%). Of the suspected cases, 76% (263 of 347) were determined to be evaluable cases of HZ, 259 (98%) by PCR and four (2%) by CEC adjudication. Two subjects each had two evaluable cases of HZ during the LTPS but, per protocol, only the first evaluable case was counted as a study endpoint in the primary and sensitivity analyses.

A HZ clinical case summary was obtained for each suspected case of HZ. The primary dermatome involved was: thoracic (48.7%), cervical (18.3%), trigeminal (14.8%; 12.1% V1), lumbar (10.5%), sacral (7.3%). . Among the 263 evaluable cases of HZ, 147 (56%) had prodromal pain, 224 (93%) had protocol-defined acute pain, and 108 (41%) had postherpetic pain, defined as a ZBPI worst pain score of three or greater more than 30 days after rash onset. Complications of HZ were infrequent; those occurring in >1% of cases were allodynia (22%), scarring (3.4%), and ocular complications (including conjunctivitis, ptosis) (<2%). Only 4.2% of

subjects were considered to be immunosuppressed at HZ diagnosis (i.e., were receiving corticosteroids or chemotherapy, had a diagnosis of malignancy, or were transplant recipients).

Safety. No serious adverse events occurred during the LTPS that were judged possibly, probably, or definitely related to the vaccination. The cumulative mortality rate was approximately 1% per year, similar to that observed in the STPS and the SPS (2, 15).

Vaccine Efficacy. The HZ burden of illness was 1.74 per 1000 person-years in the study population; 1.58 per 1000 person-years among subjects ages 60 to 69 years at SPS entry and 1.98 per 1000 person-years among subjects ≥70 years of age at SPS entry (Table 1). The incidence of protocol-defined PHN was 1.27 cases per 1000 person-years in the study population; 1.16 cases per 1000 person-years in subjects 60 to 69 years of age and 1.44 cases per 1000 person-years in subjects ≥70 years of age at SPS entry (Table 2). The incidence of HZ in the study population was 10.3 cases per 1000 person-years; 10.1 cases per 1000 person-years in subjects 60 to 69 years of age and 10.7 cases per 1000 person-years in subjects ≥70 years of age at SPS entry (Table 1) For the primary analysis, the age-year adjusted historical control HZ burden of illness was 2.77 per 1000 person-years, the historical control incidence of PHN was 1.96 cases per 1000 person-years, and the historical control incidence of HZ was 13.1 cases per 1000 person-years, and these were used as constants in the denominator for vaccine efficacy calculations. Vaccine efficacy for the three outcome measures for the LTPS population was 37.3% (95% CI: 26.7, 46.3) for the HZ burden of illness, 35.4% (95% CI: 8.8, 55.8) for the incidence of PHN, and 21.1% (95% CI: 10.9, 30.4) for the incidence of HZ (Figure 2). Vaccine efficacy for the HZ burden of illness and the incidence of PHN were similar, and showed a larger treatment effect than vaccine efficacy for the incidence of HZ.

Vaccine efficacy by year post-vaccination. The pooled analysis of the SPS and STPS published previously showed vaccine efficacy for both the HZ burden of illness and the incidence of HZ were significantly greater than zero for each year of follow-up through year five post-vaccination (4). The results for years 1 through 6 are presented again here (Table 3) for comparison with the LTPS results.

Person-years of follow-up averaged 6179 (range 5006 – 6865) in years seven through ten. Only 1475 person-years of follow-up were accrued in year 11. The 37 person-years of follow-up for 294 subjects for year 12 were excluded from the by-year analysis. The results for years 7 through 11 show decreasing vaccine efficacy over time for the HZ burden of illness and the incidence of HZ (Figure 3). Vaccine efficacy for the HZ burden of illness declined from 47.7% (95% CI: 20.9, 65.5) in year 7 to 7.9% (95% CI: -48.6, 42.9) in year 11, and vaccine efficacy for the incidence of HZ declined from 46.0% (95% CI: 28.4, 60.2) in year 7 to -1.4% (95% CI: -56.6, 38.1) in year 11 (Table 3). Vaccine efficacy for the incidence of PHN also declined from 26.3% (95% CI: -40, 66.3) in year 7 to 11.7% (95% CI: -100.0, 81.8) in year 11, with wider confidence intervals than for the other two study outcomes and only one year (year 9) in which the CI excluded zero (Table 3). Although vaccine efficacy for all three study outcomes appears to decline with time post-vaccination, the wide confidence intervals for the by-year estimates of vaccine efficacy preclude year-to-year comparisons. Nevertheless, vaccine efficacy for the HZ burden of illness and the incidence of PHN appears to persist into year ten post-vaccination; vaccine efficacy for the incidence of HZ appears to persist only through year eight following vaccination.

Discussion

In the LTPS, follow-up of a cohort of 6867 subjects who received zoster vaccine on enrollment into the SPS for a period ranging from 4.7 to 11.6 years post-vaccination, showed that zoster vaccine reduced the HZ burden of illness by 37.3%, the incidence of PHN by 35.4 %, and the incidence of HZ by 21.1%, compared to a historical control population. These estimates of zoster vaccine efficacy are 39% lower for the HZ burden of illness, 47% lower for the incidence of PHN, and 59% lower for the incidence of HZ than zoster vaccine efficacy in the SPS (61.1%, 66.5% and 51.3%, respectively), in which zoster vaccine and placebo recipients were followed from 0 to 4.9 years post-vaccination (2). The estimates of zoster vaccine efficacy from the LTPS are also 26% lower for the HZ burden of illness, 41% lower for the incidence of PHN, and 47% lower for the incidence of HZ than those from the STPS (50.1%, 60.1% and 39.6%, respectively), in which SPS vaccine recipients were followed from 3.3 to 7.8 years post-vaccination (4).

Previous analyses for each year from years 1 through 7 post-vaccination in the combined SPS and STPS populations showed that zoster vaccine efficacy for the HZ burden of illness and the incidence of HZ was statistically significant for each year through year five, with the greatest protection in the first year post-vaccination (4). The LTPS was conducted to determine whether zoster vaccine provides protection for a longer period. Analysis of the LTPS results for each year from year 7 through year 11 post-vaccination indicate that zoster vaccine efficacy continued to decline in this long-term follow-up period, but still remained statistically significant through year 8 post-vaccination. However, the wide confidence intervals for the by-year estimates of vaccine efficacy preclude definitive conclusions from the year-to-year comparisons.

The comparable mortality rates observed among vaccine and placebo recipients in the SPS and STPS, and the absence of vaccine-related adverse events supports the long-term safety of zoster vaccine (2, 4, 15).

Since the vast majority of the LTPS population was recruited from the STPS zoster vaccine recipients, it was not expected that the incidence of HZ would be lower in years seven and eight. Over the LTPS follow-up period, the HZ incidence increased each year from 7.0 cases per 1000 person-years in year seven, to 11.4 cases per 1000 person-years in year ten and 13.6 cases per 1000 per person-years in year 11. However, we do not have the statistical power to detect a significant difference between years of follow-up, thus our discussion is based largely on the trends in point estimates from the primary and supportive analyses.

There are limitations in the LTPS that are important to note. First, the selection of the LTPS population was limited by resources, permitting the inclusion of only the 12 of the 22 original SPS sites that were included in the STPS. The study was designed to provide descriptive results with no pre-specified hypotheses for vaccine efficacy. The study population was limited in size to zoster vaccine recipients who could still be contacted at the 12 sites that participated in STPS. Therefore, the study protocol was approved with sample size estimates with adequate power (>90 percent) to detect vaccine efficacy on the incidence of HZ greater than zero if the vaccine efficacy was as low as 20 percent, but the study was not powered to detect a specific time-point at which zoster vaccine efficacy fell below a pre-specified level. An age-adjusted historical-control group was used as a proxy placebo (control) group, because SPS placebo recipients were offered zoster vaccine after completion of the SPS, and thus could not serve as a placebo control

group for the LTPS. The data available for calculating historical controls was derived from placebo recipients followed in the SPS and STPS, and there was limited clinical data for modeling projected rates. Several alternative models were evaluated, and two were chosen for sensitivity analyses (16). The smaller cohort in the LTPS and the necessary use of historical controls introduced additional variability and potential bias into the LTPS results. However, sensitivity analyses support the results of the primary analysis (Figures 2 and 3).

In conclusion, there was evidence of decreasing, but persisting, zoster vaccine efficacy for the HZ burden of illness, the incidence of PHN, and the incidence of HZ in the LTPS population, compared to the SPS and STPS populations. Analysis of the LTPS results for year 7 through year 11 post-vaccination indicate that zoster vaccine efficacy continued to decline in this long-term follow-up period, but remained statistically significant through year 8 post-vaccination. These findings support the need for future prospective study of re-vaccination of zoster vaccine recipients.

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Figure 1. Screening, Enrollment and Disposition for Subjects in the Long-Term Persistence Substudy (LTPS)

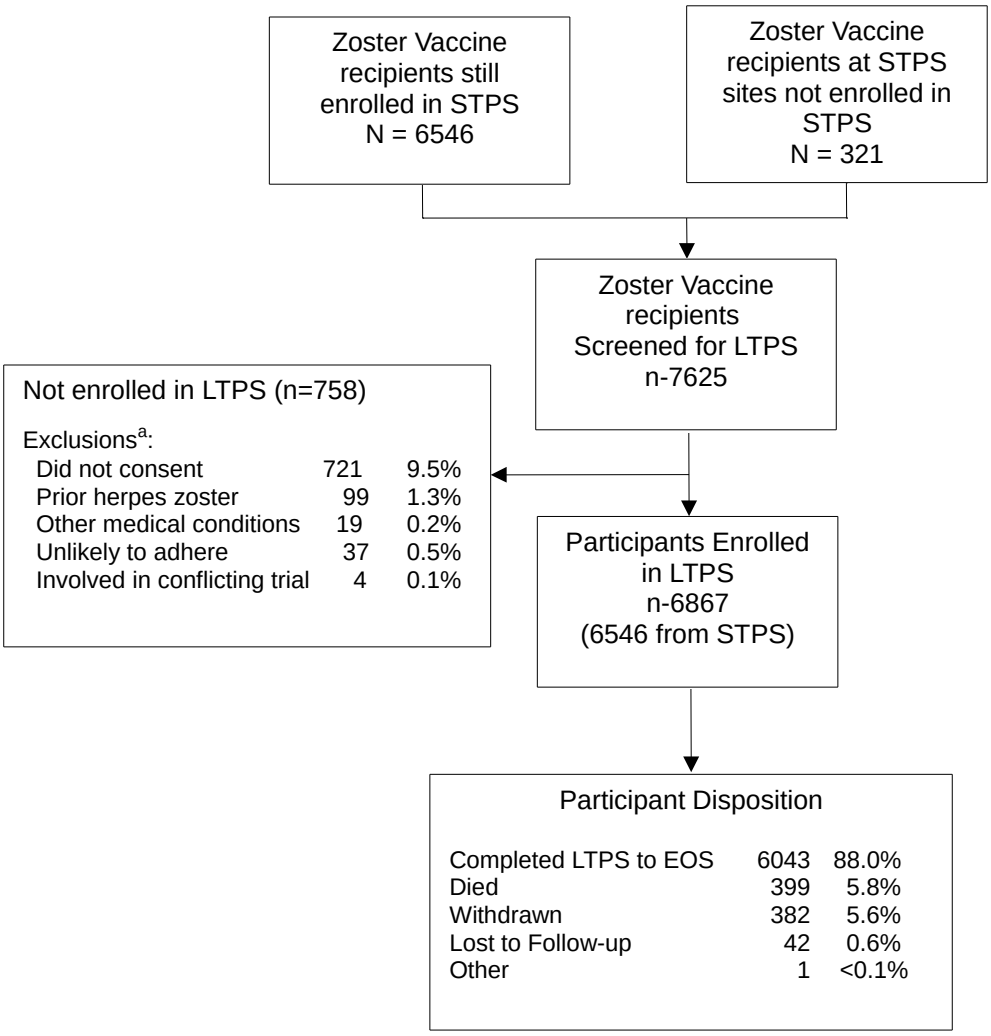
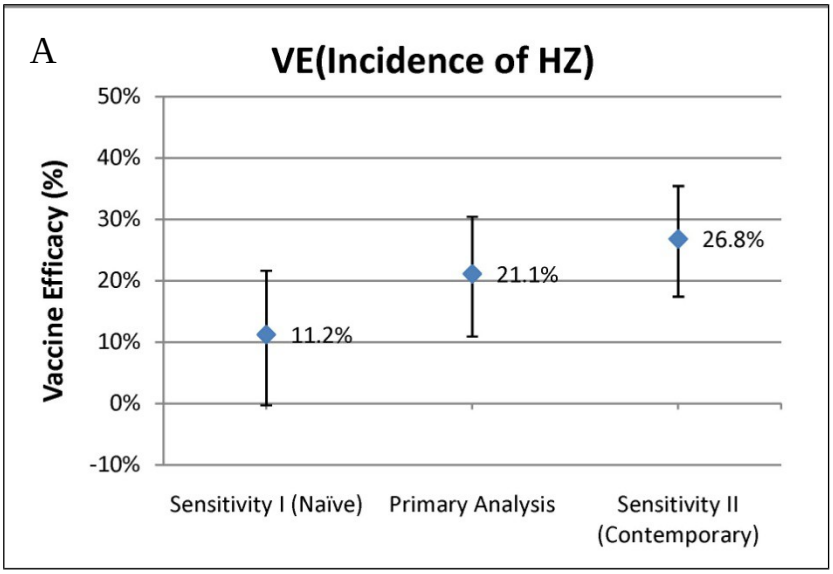
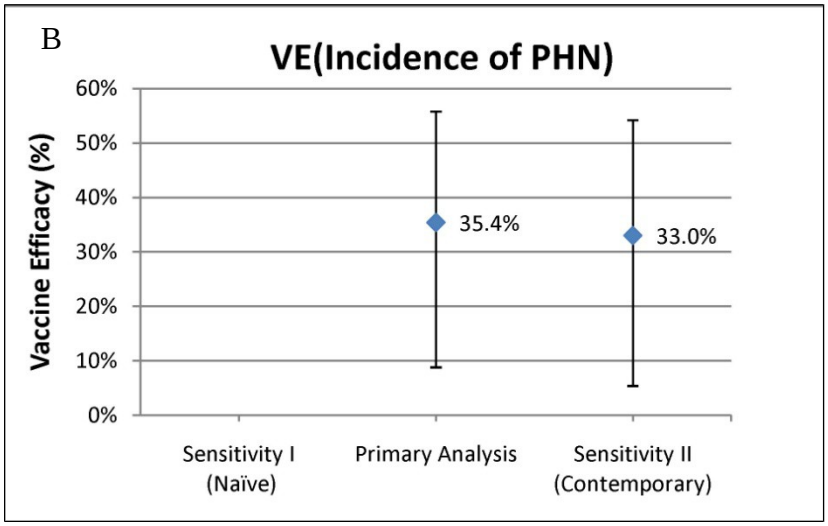


Figure 1 Legend:
[a] Reasons for not enrolling are not mutually exclusive (i.e., subjects may have had more than one reason for not enrolling in LTPS). LTPS = Long-Term Persistence Substudy, STPS =Short-Term Persistence Substudy. EOS = End of Study

Figure 2. Vaccine Efficacy for Study Outcomes for the Long-Term Persistence Substudy (LTPS) – Primary and Sensitivity Analyses.





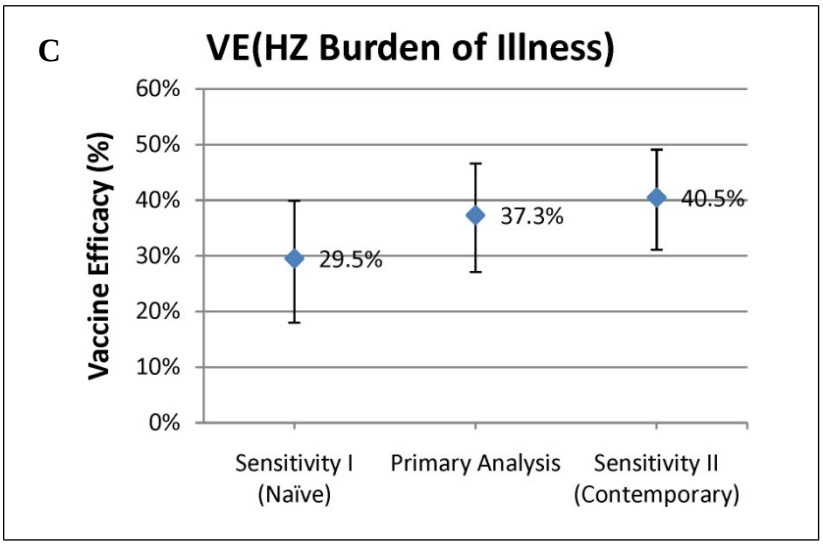
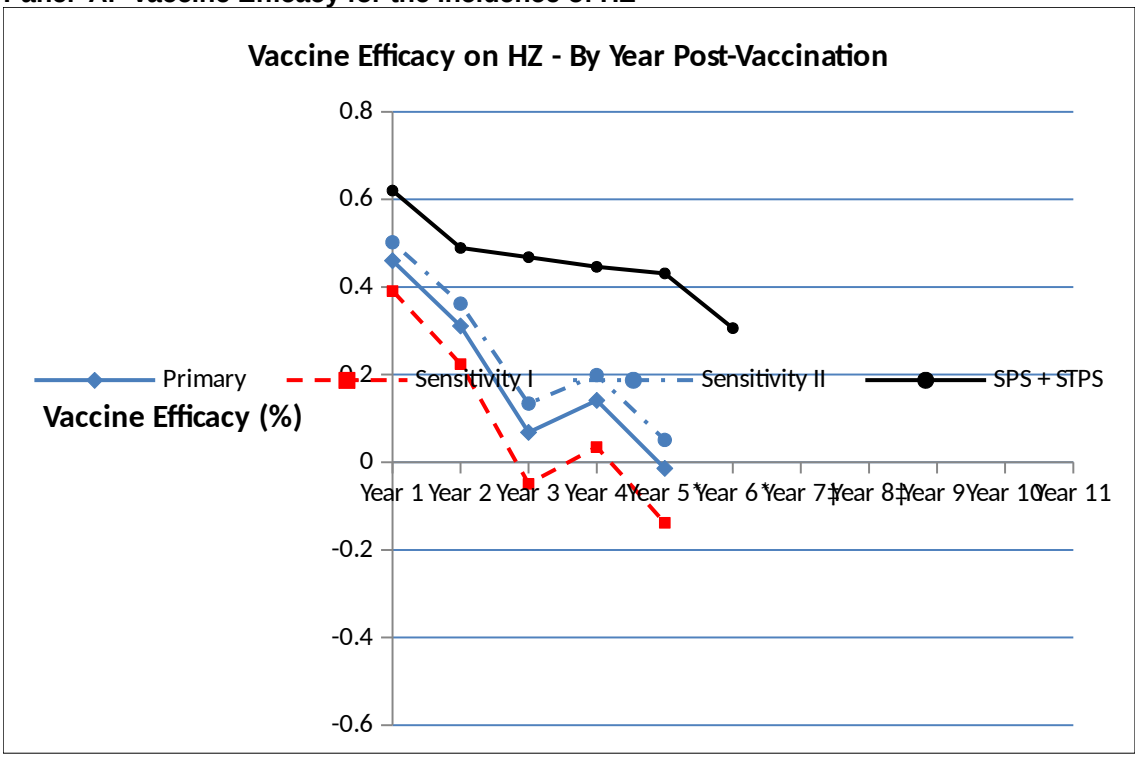
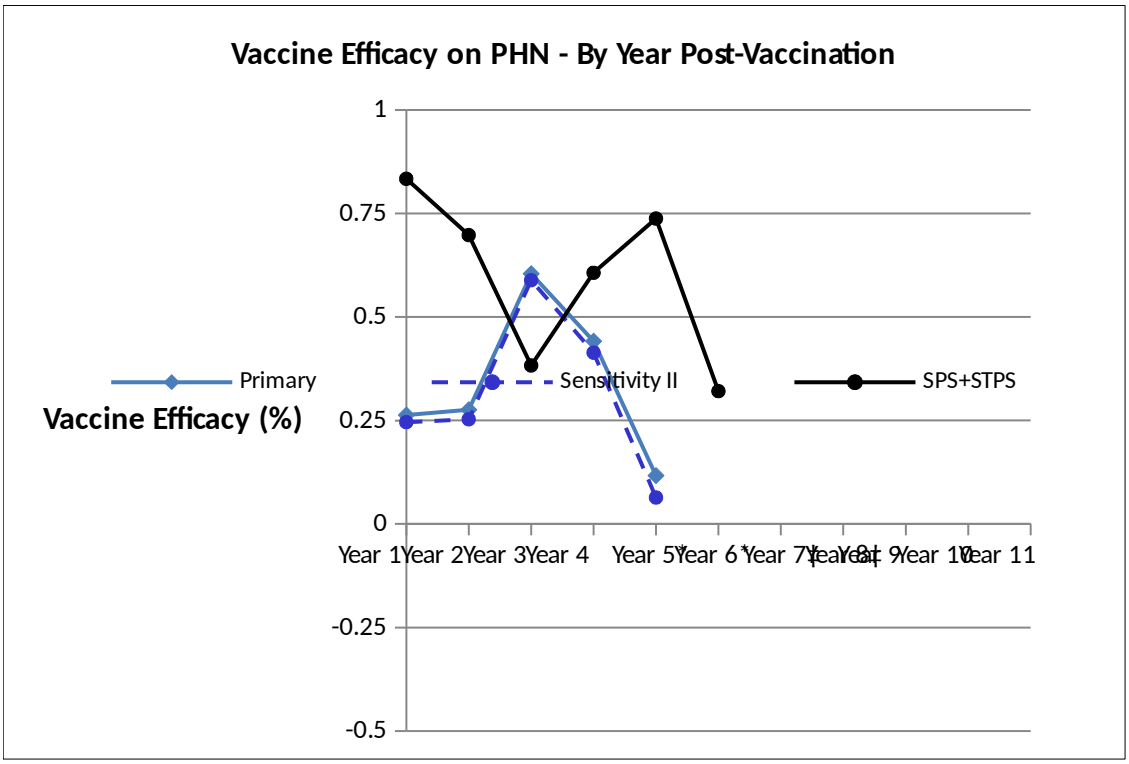


Figure 3. Vaccine Efficacy for the Three Study Outcomes by Year Post-Vaccination for the Long-Term Persistence Substudy (LTPS)

Panel A: Vaccine Efficacy for the Incidence of HZ



Panel B. **Vaccine Efficacy for the Incidence of PHN**



Panel C **Vaccine Efficacy for the HZ BOI**

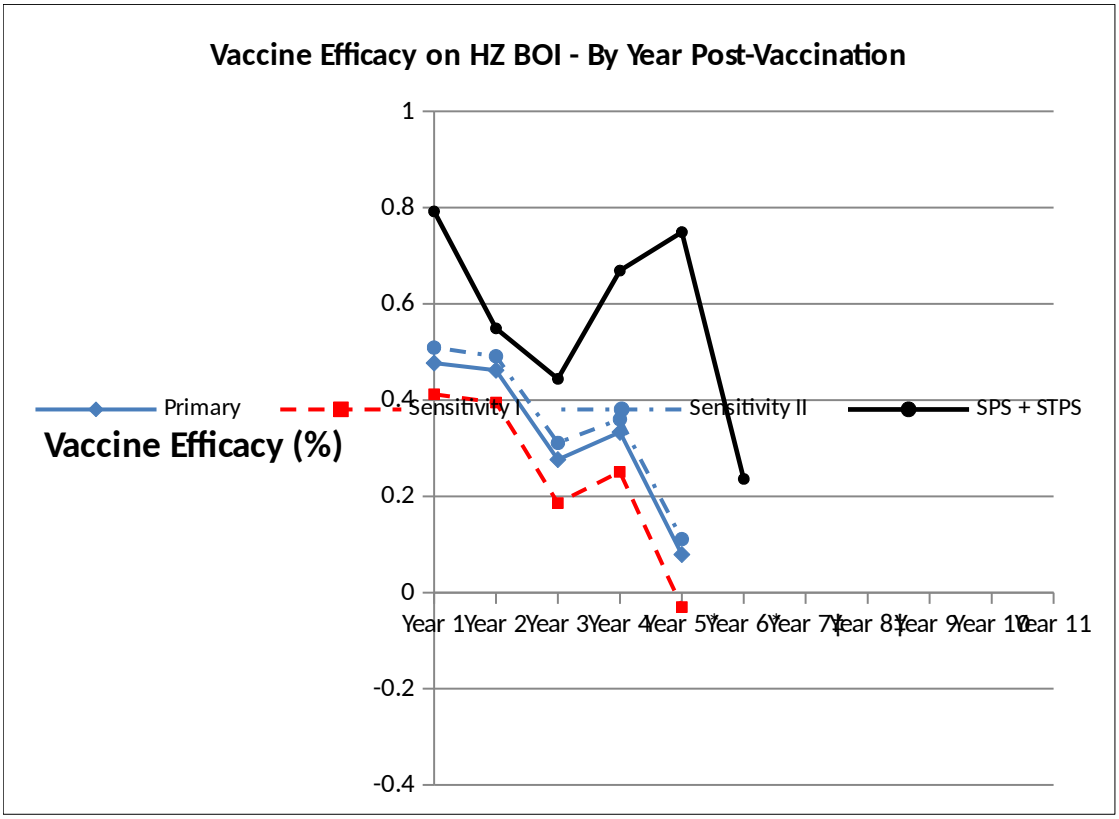


Table 1. Summary of Incidence of HZ and HZ Burden of Illness by Age Strata

	Zoster Vaccine Recipients Enrolled in LTPS (N = 6867)						
Age Group (Years)	Number of cases of HZ	Total Number of Subjects	Total Follow-Up Time (Person-Years)	Incidence Rate of HZ (Per 1000 Person-Years)	Incidence Rate of HZ (95% CI)	HZ Burden of Illness (BOI)	HZ Burden of Illness (BOI) (95% CI)
60 to 69	157	4127	15518	10.1	(8.6, 11.8)	1.58	(1.28, 1.95)
≥ 70	104	2740	9731	10.7	(8.7, 12.9)	1.98	(1.57, 2.50)
All	261	6867	25250	10.3	(9.1, 11.7)	1.74	(1.48, 2.03)

Legend: LTPS population was stratified by age at the time of randomization in SPS 60 to 69 years of age and ≥70 years of age.

Table 2. Summary of Incidence of PHN Using Protocol and Alternative PHN Definitions by Age Strata

		Zoster Vaccine Recipients (N = 6867)		
PHN Defined by Cutoff Day (After Rash Onset)	Age Group (Years)	Number of cases of PHN	Incidence Rate of PHN (Per 1000 Person-Years)	Incidence Rate of PHN (95% CI)
30 days	60 to 69	42	2.71	(1.95, 3.66)
	≥ 70	35	3.60	(2.51, 5.00)
	All	77	3.05	(2.41, 3.81)
60 days	60 to 69	23	1.48	(0.94, 2.22)
	≥ 70	20	2.06	(1.26, 3.17)
	All	43	1.70	(1.23, 2.29)
90 days†	60 to 69	18	1.16	(0.69, 1.83)
	≥ 70	14	1.44	(0.79, 2.41)
	All	32	1.27	(0.87, 1.79)
120 days	60 to 69	12	0.77	(0.40, 1.35)
	≥ 70	10	1.03	(0.49, 1.89)
	All	22	0.87	(0.55, 1.32)
182 days	60 to 69	7	0.45	(0.18, 0.93)
	≥ 70	4	0.41	(0.11, 1.05)
	All	11	0.44	(0.22, 0.78)

Legend: LTPS population was stratified by age at the time of randomization in SPS. The number of participants in the 60-69 years age stratum was 4127 followed for 15,518 person-years, and in the 70 years and older stratum, 2740 participants were followed 9731 person-years.

† The protocol definition of PHN was zoster pain or discomfort (with a ZBPI score of 3 or more) beyond 90 days after rash onset.

Table 3. Vaccine Efficacy of Zoster Vaccine Estimated for Years Post-Vaccination in the Shingles Prevention Study (SPS), the Short-Term Persistence Substudy (STPS), and the Long-Term Persistence Substudy (LTPS)

Time Period Since Randomization[†] (Years)	**Number of Person Years**	**Burden of Illness (Zoster Vaccine Group)**	**Vaccine Efficacy for HZ BOI** Point Estimate (95% CI)	**Cases of PHN (Zoster Vaccine Group)**	**Vaccine Efficacy for Incidence of PHN** Point Estimate (95% CI)	**Incidence of HZ (Zoster Vaccine Group)**	**Vaccine Efficacy for Incidence of HZ** Point Estimate (95% CI)
Year 1	17,584	0.43	79.2 (66.8, 86.9)	0.28	83.4 (56.7, 95.0)	3.9	62.0 (49.6, 71.6)
Year 2	18,869	0.78	54.9 (32.0, 70.1)	0.37	69.8 (27.3, 89.1)	5.4	48.9 (34.7, 60.1)
Year 3	15,181	0.98	44.4 (17.6, 62.5)	0.66	38.3 (-44.7, 75.0)	6.1	46.8 (31.1, 59.2)
Year 4[†]	6264	0.76	66.9 (37.5, 82.5)	0.64	60.7 (-36.3, 91.0)	7.8	44.6 (20.5, 61.8)
Year 5[†]	3180	0.68	74.9 (48.6, 87.7)	0.63	73.8 (-37.8, 97.3)	8.2	43.1 (5.1, 66.5)
Year 6[†]	4581	1.81	23.6 (-58.1, 63.1)	0.83	32.0 (-100.0, 87.3)	9.9	30.6 (-6.0, 54.6)
Long-Term Persistence							
Year 7[††]	6865	1.37	47.7 (20.9, 65.5)	1.31	26.2 (-40.1, 66.3)	7.0	46.0 (28.4, 60.2)
Year 8[††]	6564	1.46	46.2 (25.8, 61.0)	1.37	27.7 (-37.3, 66.9)	9.0	31.3 (11.3, 47.7)
Year 9	6280	2.04	27.6 (4.5, 45.1)	0.80	60.4 (7.7, 87.2)	12.2	6.7 (-16.6, 26.4)
Year 10	5006	1.95	33.3 (1.5, 54.8)	1.20	44.2 (-21.5, 79.5)	11.4	14.1 (-11.3, 34.9)
Year 11	1475	2.79	7.9 (-48.6, 42.9)	2.03	11.7 (-100.0, 81.8)	13.6	-1.4 (-56.6, 38.1)

Results of the primary analysis are reported here.

[†] For the calculation of vaccine efficacy (VE), HZ events and person-years of follow-up were pooled for SPS and STPS for Years 4 and Year 5 post-vaccinations. For Year 4, person-years were 97% from SPS and 3% from STPS. For Year 5, person years were 16% from SPS and 84% from STPS. For Years 6 100% of the events and person-years were from STPS subjects.

[††] For the calculation of vaccine efficacy (VE) in Years 7 and Year 8, HZ events and person-years of follow-up for the zoster vaccine group were pooled for STPS and LTPS, and historical controls determined from the placebo group results from SPS. For Year 7, 31% [2136/6861] person-years were from STPS and 69% [4725/6861] were from LTPS. For Year 8, 8% [542/6577] person-years were from STPS and 92% [6035/6577] were from LTPS.

, For Years 9 to 11, HZ events and person-years of follow-up for the zoster vaccine group were all obtained from the LTPS, and historical controls determined from the placebo group results from SPS..

SPS = Shingles Prevention Study (primary efficacy study for the zoster vaccine). STPS = Short-Term Persistence Substudy.

LTPS = Long –Term Persistence Substudy.