The Durability of Vaccine Efficacy on the Incidence of Herpes Zoster Provided by ZOSTAVAX

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Overview

ZOSTAVAX is licensed in US for the prevention of herpes zoster (HZ) in persons ≥60 years of age based on the Shingles Prevention Study (SPS). A subset of SPS subjects was subsequently enrolled into an extension study (Short-Term Persistence Study or STPS) to collect longer-term vaccine efficacy (VE) data. To assess the long-term cost-effectiveness of ZOSTAVAX, the durability of VE was evaluated based on data from SPS/STPS. The durability of VE on incidence of HZ (VE_{HZ}) is discussed here.

Introduction

- ZOSTAVAX was shown to be efficacious in preventing HZ, PHN, and lowering HZ BOI in persons ≥60 years of age in the SPS (Oxman *et al* 2005)
- It is critical to consider the durability of VE on incidence of HZ, when assessing the long-term cost-effectiveness of ZOSTAVAX
- The methodology for evaluating the durability of VE on HZ will be discussed
- Predicted mean duration of protection for persons ≥60 years of age (at vaccination) ranged from 12 years to lifelong, based on the SPS (Pellissier *et al 2007)*
- Additional data from the STPS is available since then (Schmader *et al* 2008)

Clinical Study Results

Vaccine Efficacy Results: Statistical Analysis of Annual Incidence of HZ Cases (SPS + STPS)

Time Period Since Randomization† (Years)	Zoster Vaccine (N = 19270)				Placebo (N = 19276)				Vaccine Efficacy for Incidence of HZ
	n	m	Total Follow-Up Time (Person-Years)	Observed Incidence Rate of HZ (Per 1000 Person-Years)	n	m	Total Follow-Up Time (Person-Years)	Observed Incidence Rate of HZ (Per 1000 Person-Years)	Point Estimate (95% CI)
Year 1	69	19254	17584	**3.92**	181	19247	17539	**10.32**	**0.62 (0.50, 0.72)**
Year 2	102	19024	18869	**5.41**	198	18948	18731	**10.57**	**0.49 (0.35, 0.60)**
Year 3	92	18692	15181	**6.06**	171	18494	14998	**11.40**	**0.47 (0.31, 0.59)**
Year 4	49	11686	6264	**7.82**	87	11473	6158	**14.13**	**0.45 (0.21, 0.62)**
Year 5	26	7178	3180	**8.18**	42	6874	2921	**14.38**	**0.43 (0.05, 0.67)**
Year 6	48	7085	4848	**9.90**	47	6051	3294	**14.27**	**0.31 (-0.06, 0.55)**
Year 7	12	4054	2136	**5.62**	11	2237	886	**12.42**	**0.55 (-0.13, 0.82)**
Year 8	1	542	112	**8.97**	0	96	13	**0.00**	----

† Randomization into the SPS.
N = Number of subjects randomized.
n = Number of evaluable HZ cases that occurred during the time period in the pooled population.
m = Number of subjects followed during the time period in the pooled population.

Vaccine Efficacy Results: Statistical Analysis of Incidence of HZ Cases by Age Group (SPS+STPS)

Age Group† (Years)	Zoster Vaccine (N = 19270)				Placebo (N = 19276)				Vaccine Efficacy with Respect to HZ
	n	m	Total Follow-Up Time (Person-Years)	Estimated Incidence Rate of HZ (Per 1000 Person-Years)	n	m	Total Follow-Up Time (Person-Years)	Estimated Incidence Rate of HZ (Per 1000 Person-Years)	Point Estimate (95% CI)
60 to 69	168	10370	37213	**4.52**	390	10356	34956	**11.16**	**0.60 (0.51, 0.66)**
≥70	231	8884	30957	**7.46**	347	8891	29582	**11.73**	**0.36 (0.25, 0.46)**

N = Number of subjects randomized.
n = Number of evaluable HZ cases in the respective age groups of the pooled population.
m = Number of subjects in the respective age groups of the pooled population.

Observation of the Vaccine Efficacy Results

- Vaccine Efficacy on HZ may potentially be affected by time since vaccination, as well as age
- Define waning effect as decrease in vaccine efficacy due to time since vaccination (independent of age)
- Question: Is the decrease in VE over time observed due to time since vaccination or aging, or both?
- When age at vaccination is used, the age and time effects may be confounded with each other. Need to evaluate these two potential effects separately
- Concurrent age can be used, which is defined as the current age at follow-up.
- Objective: To evaluate the durability of VE on HZ based on data from the SPS as well as STPS, using concurrent age, instead of age at vaccination

Statistical Methods

- Data: Combination of the SPS and STPS data
- Follow-up Data Handling: subject follow-up data are parsed into different bins defined by (concurrent) age and year (from vaccination)
- Model Used: Poisson regression with number of HZ cases in each bin as the dependent variable, follow-up time in the bin as off-set parameter and the following potential independent variables
  - Age (concurrent)
  - Year since vaccination
  - Whether in 1st year post vaccination
  - Treatment
  - Treatment x Age (concurrent)
  - Treatment x Whether in 1st year post vaccination
  - Treatment x Year since vaccination

Interpretation of the Model Parameter Estimates

- Treatment (ZOSTAVAX vs.Placebo): exponential of the parameter estimate indicates the risk ratio (of developing HZ) between ZOSTAVAX and Placebo, after adjusting for all other parameters
- Treatment by Age (or year) interaction: exponential of the parameter estimate indicates the relative change in the risk ratio (of HZ) between ZOSTAVAX and Placebo per year of age (or year of time since vaccination), after adjusting for all other parameters
- Note that Vaccine Efficacy = 1 – Risk Ratio
- A positive (or negative) parameter estimate of the interaction term between a covariate (age or time) and treatment indicates that risk ratio between ZOSTAVAX and placebo increases (or decreases) with increasing covariate value

Analysis Results

Poisson Regression Models: Parameter Estimate (p-Value)

Parameter	Model I	Model II	Model III	Model IV	Model V
Concurrent Age*	0.0075 (0.189)	0.0042 (0.472)	0.0035 (0.544)	0.0043 (0.470)	0.0043 (0.461)
Time Since Vac.		0.0680 (0.005)	0.0816 (<0.001)	0.0744 (0.017)	0.0726 (0.002)
1st Year Post Vac				-0.0368 (0.740)	-0.0327 (0.745)
Treatment	-1.2337 (<0.001)	-1.3151 (<0.001)	-1.2445 (<0.001)	-1.4290 (<0.001)	-1.4273 (<0.001)
Treatment by Concurrent Age	0.0414 (<0.001)	0.0392 (<0.001)	0.0410 (<0.001)	0.0390 (<0.001)	0.0389 (<0.001)
Treatment by Time Since Vac.		0.0322 (0.390)		-0.0042 (0.929)	
Treatment by 1st Year Post Vac				0.2776 (0.153)	0.2677 (0.093)
Deviance	489.2	469.7	470.5	467.3	467.3

*(age-59) is applied

Vaccine Efficacy Calculation By Different Models

Model I:

$$VE = 1 - e^{-1.2337 + 0.0414 \times (Age - 59)}$$

Model II:

$$VE = 1 - e^{-1.3151 + 0.0392 \times (Age - 59) + 0.0322 \times YearSinVac}$$

Model III:

$$VE = 1 - e^{-1.2445 + 0.0410 \times (Age - 59)}$$

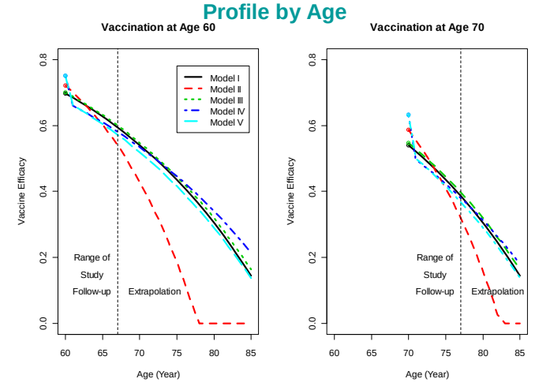
Model IV:

$$VE = 1 - e^{-1.4290 + 0.0390 \times (Age - 59) - 0.0042 \times YearSinVac + 0.2776 \times I_{>1Year}}$$

Model V:

$$VE = 1 - e^{-1.4273 + 0.0389 \times (Age - 59) + 0.2677 \times I_{>1Year}}$$

Example of Predicted/Extrapolated Vaccine Efficacy Profile by Age



Conclusion

- There is a robust statistically significant age effect on VE
- The effect of time since vaccination on VE (waning effect) is not statistically significant, which may potentially due to the fact that the duration of follow-up is ~7 years (instead of a longer period). And majority of decreasing in VE over time may be due to the initial drop in VE during the 1st year post vaccination.
- It is difficult to have a long-term efficacy follow-up in a clinical trial setting post licensure (size and duration of SPS/STPS is unprecedented)
- While all five models fit the data well, none is perfect. And they provide a reasonable range for the durability of VE
- It is critical to consider the durability of VE on HZ, along with HZ burden-of-illness (BOI) and postherpetic neuralgia (PHN), when assessing the long-term cost-effectiveness of ZOSTAVAX. While only HZ is considered here, clinical data indicated the durability of VE on HZ BOI and PHN

References

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