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Cost-Effectiveness of Herpes Zoster Vaccine for Persons Aged 50 Years

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Background: Each year, herpes zoster (HZ) affects 1 million U.S. adults, many of whom develop postherpetic neuralgia (PHN). Zoster vaccine is licensed for persons aged 50 years or older, but its cost-effectiveness for those aged 50 to 59 years is unknown.

Objective: To estimate the cost-effectiveness of HZ vaccine versus no vaccination.

Design: Markov model.

Data Sources: Medical literature.

Target Population: Adults aged 50 years.

Time Horizon: Lifetime.

Perspective: Societal.

Intervention: HZ vaccine.

Outcome Measures: Number of HZ and PHN cases prevented and incremental cost per quality-adjusted life-year (QALY) saved.

Results of Base-Case Analysis: For every 1000 persons receiving the vaccine at age 50 years, 25 HZ cases and 1 PHN case could be prevented. The incremental cost-effectiveness ratio (ICER) for HZ vaccine versus no vaccine was $323 456 per QALY.

Results of Sensitivity Analysis: In deterministic and scenario sensitivity analyses, the only variables that produced an ICER less than $100 000 per QALY were vaccine cost (at a value of $80) and the rate at which efficacy wanes. In probabilistic sensitivity analysis, the mean ICER was $500 754 per QALY (95% CI, $93 510 to $1 691 211 per QALY). At a willingness-to-pay threshold of $100 000 per QALY, the probability that vaccination would be cost-effective was 3%.

Limitation: Long-term effectiveness data for HZ vaccine are lacking for 50-year-old adults.

Conclusion: Herpes zoster vaccine for persons aged 50 years does not seem to represent good value according to generally accepted standards. Our findings support the decision of the Advisory Committee on Immunization Practices not to recommend the vaccine for adults in this age group.

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Herpes zoster (HZ), also known as shingles, affects approximately 1 million Americans every year, with almost 1 in 3 expected to have HZ during his or her lifetime (1). The incidence and severity of HZ increase with age, with a sharp increase in incidence after age 50 years (1, 2). Postherpetic neuralgia (PHN), the persistence of pain beyond 3 months, is the most common complication, occurring in 8% to 32% of patients (3). Although prompt antiviral therapy reduces the acute symptoms of HZ, treatment is generally not effective in preventing PHN (4, 5). Consequently, control efforts have focused on prevention.

To date, only the live attenuated Oka strain varicella-zoster vaccine has been licensed for prevention of HZ and PHN in older adults. The SPS (Shingles Prevention Study), STPS (Short-Term Persistence Substudy), and LTPS (Long-Term Persistence Substudy) have shown that the vaccine is effective in reducing HZ incidence, PHN incidence, and burden of illness among persons aged 60 years or older and that efficacy decreases over time (6–8). In 2011, the zoster vaccine live (Zostavax; Merck) was also licensed for adults aged 50 to 59 years on the basis of findings from ZEST (Zostavax Efficacy and Safety Trial) (9). However, in 2014, the Advisory Committee on Immunization Practices declined to recommend vaccination for adults in this age group. One consideration, based on an unpublished model (10), was the cost-effectiveness of the vaccine.

Many economic evaluations of HZ vaccine have been conducted in North America and Europe, but most of them considered only persons aged 60 years or older (11). The cost-effectiveness for younger patients is strongly influenced by the long-term efficacy of the vaccine, which has only recently been reported and was not previously incorporated into decision models (6). Compared with older age groups, persons aged 50 to 59 years have a lower incidence of HZ and a lower probability of PHN once they develop HZ (1). Therefore, the vaccine may not be cost-effective in this age group unless it continues to provide immunity at older ages. A recommendation to vaccinate adults aged 50 to 59 years would, in essence, be a de facto recommendation to vaccinate at age 50 years because patients would become eligible for the intervention when they reach that age. To provide additional information for decision making, our study aimed to analyze the cost-effectiveness of HZ vaccine for immunocompetent adults aged 50 years by using recently published data on vaccine efficacy and persistence.

Methods

We updated a previously published Markov decision model (**Appendix Figures 1** and **2**, available at www.annals.org) that was developed to compare the cost-effectiveness of HZ vaccine versus no vaccination for healthy immunocompetent adults (12). We maintained the model structure but updated the inputs to reflect vaccine-related and epidemiologic data for persons aged 50 to 59 years. The entire cohort entered the model in the "healthy" state at age 50 years and was followed for a lifelong time horizon. The length of the Markov cycle was 1 year. The cohort moved between health states with transition probabilities (**Table 1**) until the last cohort member died at age 120 years. The vac-

EDITORS' NOTES

Context

Herpes zoster (HZ) vaccine is licensed for persons aged 50 years or older, but the Advisory Committee on Immunization Practices (ACIP) recommends it only for those aged 60 years or older.

Contribution

In a Markov model, use of HZ vaccine at age 50 years resulted in an incremental cost-effectiveness ratio of more than $300 000 per quality-adjusted life-year, an amount more than 3 times that generally considered reasonable.

Caution

Many model parameters were based by necessity on data from studies of persons aged 60 years or older.

Implication

The current ACIP guideline not to use HZ vaccine among persons aged 50 to 59 years seems appropriate.

cinated group had a reduction in disease incidence and complications proportional to vaccine efficacy. Disutility of complications was assigned at the time of occurrence unless they resulted in permanent disability (for example, monocular blindness), in which case they resulted in a permanent decrement in annual utility. Complications (including hospitalization, PHN, and ophthalmic and otic complications) were assumed to be independent, and more than one could occur at the same time. Outcomes included costs and effectiveness (the number of HZ cases, PHN cases, and quality-adjusted life-years [QALYs]) for each strategy. The incremental cost-effectiveness ratio (ICER) was estimated as the incremental cost (in dollars) divided by the incremental increase in effectiveness (in QALYs) between the strategies. The study was conducted from the societal perspective, with both costs and QALYs discounted at 3% per year. All costs were expressed in 2014 U.S. dollars, adjusted for inflation using the medical care component of the Consumer Price Index (31). The model was developed in TreeAge Pro 2014 (TreeAge Software).

Model Inputs and Assumptions

Data used for the model were derived primarily from U.S.-based studies to reflect the epidemiology, utilities, and QALYs of the general U.S. population. Table 1 presents estimates for the base-case analysis and deterministic and probabilistic sensitivity analyses.

Epidemiologic Parameters

Several contemporary studies have examined age- and sex-specific incidence rates of HZ in the United States and found increasing rates over time across all age groups (1, 13, 32, 33). The reason for this trend is unknown, but it predates the widespread use of varicella vaccine. It most likely represents increasing awareness among patients and physicians such that patients are now more likely to seek care and physicians are more likely to make the diagnosis. The decrease in incident varicella due to childhood vaccination may also have contributed through a reduction in natural boosting (34, 35). We used data from 1993 to 2006 reported by Leung and colleagues (13) to fit several linear regressions of age- and sex-specific incidence rates versus time ($R^2 > 0.90$ in all cases) and estimated the incidence rates for 2010 (Appendix, available at www.annals.org). Because incidence cannot increase indefinitely, for the base case we assumed that incidence rates would plateau after 2010, by which time HZ was well-publicized and varicella vaccination for children had been required for school attendance for more than a decade (36). We also conducted a sensitivity analysis in which the incidence continued to increase for 5 more years (to 2015) before plateauing. Furthermore, we assumed that the annual risk for HZ recurrence was the same for subsequent HZ episodes as for the first one (37).

The age-specific incidence rates of PHN (defined as pain persisting ≥3 months after HZ onset) were based on the SPS for persons aged 60 to 69 years and those aged 70 years or older (7). Because PHN was rare in ZEST, we estimated its incidence rate for persons aged 50 to 59 years by pooling results from 3 observational studies (1, 14, 15). The rates of hospitalization due to HZ were based on validated epidemiologic data (20). The probability of death due to HZ by age was estimated from mortality data for 1999 to 2012 from the Centers for Disease Control and Prevention WONDER database (21). The proportion of PHN lasting at least 12 months was based on the largest prospective cohort study and was assumed to equal that for persons aged 60 to 69 years (14). Derivation of other complication rates (ophthalmic complications, monocular blindness, herpes oticus, and monaural deafness) has been described previously (12). Background age- and sex-specific mortality rates were based on 2010 U.S. life tables (38). The sex distribution of 50-year-old adults mirrored that of the U.S. population in 2013 (39).

Vaccine-Related Parameters

ZEST reported vaccine efficacy to 1.5 years, but no long-term efficacy data are available for persons aged 50 to 59 years (9). The LTPS reported efficacy for up to 11.6 years after vaccination, but results were limited to persons aged 60 years or older (6). To estimate efficacy for those aged 50 years, we combined both data sources. First, we fit a linear function to the LTPS data (Figure 1). To reduce noise generated by the small number of participants in the last 4 years of the LTPS, we plotted the combined efficacy from years 4.7 to 11.6 at 7.7 years, based on a weighted average. The R^2 value for the line was 0.93 (Appendix). We then used the slope of this function to represent the rate of decrease in efficacy and assumed that it waned at the same rate regardless of age at vaccination. However,

Table 1. Epidemiologic, Quality-of-Life, and Cost Inputs: Baseline Values, Ranges, and Parameters for Distributions Used in the Base-Case and Sensitivity Analyses

Variable	Base-Case Value	Sensitivity Analysis		Reference
		Range for 1-Way Analysis	PSA Distribution*	
HZ incidence per 1000 person-years			β	13
Male				
Aged 50–59 y	3.8	3.6 to 4.0	(2394; 628 846)	
Aged 60–69 y	6.3	5.9 to 6.6	†	
Aged ≥70 y	9.9	9.3 to 10.5	†	
Female				
Aged 50–59 y	6.1	5.9 to 6.4	(2699; 441 208)	
Aged 60–69 y	9.1	8.6 to 9.5	†	
Aged ≥70 y	13.2	12.1 to 14.3	†	
Complications, %			β	
PHN (given HZ)				
Aged 50–59 y	0.038	0.023 to 0.053	(22.93; 310.07)	1, 14, 15
Aged 60–69 y	0.069	0.042 to 0.096	†	7
Aged 70–79 y	0.185	0.142 to 0.228	†	7
PHN ≥12 mo			(18.54; 22.45)	14
Aged <70 y	0.31	0.06 to 0.56	†	
Aged ≥70 y	0.52	0.34 to 0.70	†	
Ophthalmic complications	0.022	0.012 to 0.032	(18.97; 839.02)	16
Monocular blindness (given ophthalmic complications)	0.039	0.011 to 0.067	(6.96; 173.03)	17, 18
Herpes oticus	0.002	0 to 0.005	(1.99; 856)	16
Monaural deafness (given herpes oticus)	0.069	0.013 to 0.12	(5.43; 73.56)	19
Hospitalization (given HZ)				20
Aged 50–59 y	0.006	0 to 0.013	(2.99; 495)	
Aged 60–69 y	0.013	0.005 to 0.021	†	
Aged 70–79 y	0.018	0.011 to 0.026	†	
Aged ≥80 y	0.055	0.042 to 0.068	†	
Deaths due to HZ per 100 000 cases			β	21
Aged 50–59 y	1.26	0.86 to 1.67	(37; 2 927 644)	
Aged 60–69 y	2.22	1.72 to 2.72	†	
Aged 70–79 y	6.18	5.32 to 7.03	†	
Aged 80–89 y	23.96	21.88 to 26.03	†	
Aged ≥90 y	152.13	143.76 to 160.5	†	
Mean duration of hospitalization, *d*	4.7	4.4 to 4.9	Normal (4.73; 0.59)	22
Vaccine efficacy			Normal	
Waning rate (slope)	−0.0544	−0.072 to −0.037	(−0.0544; 0.0066)	6
First-year efficacy	0.698	0.541 to 0.806	(−1.196; 0.2084)‡	9
Adverse effect			β	9
Local reaction	0.64	0.63 to 0.65	(7088; 4004)	
Serious reaction	0.001	0 to 0.003	(0.96; 957.48)	
Utility			β	
Monocular blindness	0.92	0.885 to 0.948	(4.19; 0.36)	23
Monaural deafness	0.97	0.958 to 0.982	(660.69; 21.13)	24
PHN after 6 mo	0.67	0.618 to 0.722	(20.45; 10.07)	25
Short-term illness, *QALYs lost*			β	
Acute HZ				1, 9, 26
Aged 50–59 y	0.0054	0 to 0.0167	(0.87; 161.32)	
Aged 60–69 y	0.0129	0.0049 to 0.0207	†	
Aged ≥70 y	0.0216	0.0144 to 0.0286	†	
Hospitalization	0.0129	0.012 to 0.013	NA	Length of stay
Local reaction	0.0001	0 to 0.0003	(64; 640 000)	Assumption
Serious reaction	0.0082	0.003 to 0.016	(64; 7804)	22
Direct medical costs, *$/case*			γ	
Acute HZ	387	298 to 568	(7.11; 0.02)	12
PHN	762	651 to 906	(7.11; 0.009)	12
Ophthalmic complications	15 158	11 118 to 17 852	(7.11; 4.69)	12
Herpes oticus	481	135 to 943	(7.11; 0.015)	12
Hospitalization	7977	7477 to 8235	(7.11; 8.91)	22
Serious reaction	6609	6442 to 6703	(7.11; 0.001)	22

Continued on following page

Table 1–Continued

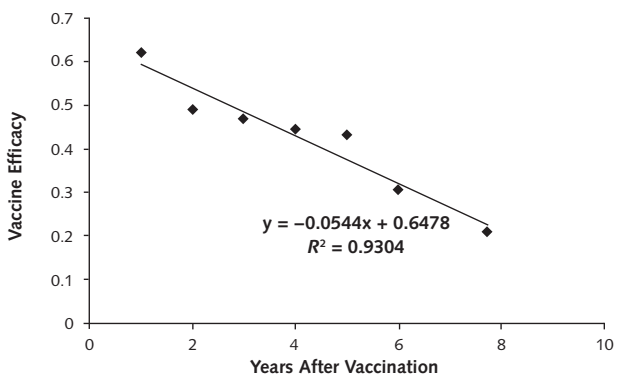
Variable	Base-Case Value	Sensitivity Analysis		Reference
		Range for 1-Way Analysis	PSA Distribution*	
Indirect cost, *$/case*			γ	27, 28
Aged 50–54 y	2513	1874 to 3152	(59.42; 0.023)	
Aged 55–59 y	2566	1913 to 3218	†	
Aged 60–64 y	4678	3373 to 5982	†	
Aged ≥65 y	4409	3179 to 5639	†	
Vaccine price, *$*	174	0 to 250	γ (64; 0.36)	29
Vaccine administration costs, *$*	25	15 to 35	γ (64; 2.55)	30

HZ = herpes zoster; NA = not applicable; PHN = postherpetic neuralgia; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life-year; ZEST = Zostavax Efficacy and Safety Trial.
* First and second values in parentheses correspond to α and β in β distribution, κ and θ in γ distribution, and mean and SD in normal distribution.
† For model inputs with age-specific values, the distribution was first defined for one age group, which was considered as the reference. Distributions for remaining age groups were determined by multiplying relative likelihood ratios among these ages and the reference age by the reference distribution. Because the value was drawn randomly from the distribution in PSA, this definition of distributions ensured that the probabilistic values of different age groups had the appropriate relative magnitudes compared with one another as when they were deterministic.
‡ Because the efficacy was estimated as 1 − log(RR) in ZEST (9), where RR was the rate ratio of having HZ in vaccinated and unvaccinated groups, we defined the distribution of log(RR) instead. Values in parentheses were the mean and SD of log(RR) estimated from ZEST.

because the initial efficacy in ZEST was higher than in the SPS, we set the intercept of the function for decreasing efficacy to match that of ZEST. The final efficacy function was y = 0.752 − 0.0544x, where *x* was the number of years after vaccination. Vaccine efficacy was not allowed to decrease below zero.

In addition, ZEST reported no significant difference in the mean severity of HZ cases between vaccinated and unvaccinated participants (9). The same was true for persons aged 60 to 69 years in SPS. Therefore, modeled vaccine efficacy was limited to reduction of HZ incidence. There was no reduction in burden-of-illness scores or PHN beyond that related to reduced HZ incidence. Although the vaccine offers additional protection against PHN to patients aged 70 years or older (40), there was no vaccine benefit after age 65 years in our model because of decreasing efficacy when the vaccine is administered at age 50 years.

Figure 1. Reduction in vaccine efficacy, by number of years after vaccination.



The linear line was estimated using data from the Long-Term Persistence Substudy (6) for herpes zoster vaccine among persons aged ≥60 y.

QALYs

Utility estimates have been described previously (12). We converted burden-of-illness scores from ZEST into utilities based on the findings of Coplan and colleagues (9, 12, 26). We assumed that serious vaccine reactions were equivalent to other allergic reactions that result in a 3-day hospitalization (22) and assigned those days a utility of zero. All utilities were adjusted for age on the basis of the 2001 Medical Expenditure Panel Survey and the 2001 National Health Interview Survey (41).

Costs

Costs were culled from various sources. Vaccine cost included the current price for the private sector as published on the Centers for Disease Control and Prevention Web site (29) and an administration cost based on the national payment amount (carrier locality code 0000000) for Medicare (30). In the SPS, vaccine local reactions comprised mostly upper arm soreness and tenderness, which were generally minimal and were assumed not to incur any costs. Serious vaccine reactions were assumed to incur the same costs as other allergic reactions necessitating hospitalization (22). Costs of acute HZ, PHN, ocular complications, and herpes oticus were drawn from our previous analysis (12) and inflated to 2014 dollars (31). The productivity loss associated with HZ and PHN was estimated from a U.S.-based telephone survey of patients with HZ that reported productivity loss by age (42). Because there were no data for persons aged 65 years or older, we assumed that their average number of hours lost due to absenteeism and presenteeism was the same as for persons aged 60 to 64 years. To estimate age-specific average wage rates, the U.S. average wage rate for all occupations–$22.71 per hour (28)–was multiplied by age-specific weights, which were calculated as the ratios of age-specific median weekly earnings to the median weekly earnings of all persons aged 16 years or older (43). The number of

hours lost was then multiplied by these age-specific wage rates to derive the age-specific indirect costs. The productivity loss was then adjusted for the percentage of the employed age-specific population (44). Finally, we used the latest data (from 2012) from the Healthcare Cost and Utilization Project Web site to estimate the duration and cost of hospitalization due to HZ (22).

Sensitivity Analysis

To assess methodological and structural uncertainties, we conducted several scenario analyses. First, we compared the relative cost-effectiveness of HZ vaccine at different ages of vaccination (1-year increments) in the range of 50 to 59 years. Second, HZ incidence was allowed to continue increasing until 2015 before plateauing. Third, vaccine efficacy was assumed to decrease at half the rate of the base case. Fourth, we assumed that vaccine efficacy remained stable for 10 years and then decreased at the same rate as in the base case. Fifth, we considered different booster options for comparison (vaccine at age 50 years with a booster at age 55 or 60 years). Because no booster is available and data on long-term efficacy of boosters will not be available for at least a decade, we assumed that the booster was the same as the initial vaccination in terms of cost, effectiveness, adverse effects, and duration and that adherence would be 100%. Finally, we assumed that the vaccine offered protection against PHN even after the effect on incidence decreased. This mirrors what has been observed in patients older than 70 years but has not been observed in younger patients (6, 7).

To assess parameter uncertainties, we conducted deterministic sensitivity analysis for all model inputs with the ranges specified in Table 1. A tornado diagram was used to present the factors with the most influence on the ICER (dollars per QALY saved). In addition, we performed multivariate probabilistic sensitivity analysis with 10 000 iterations of Monte Carlo simulation. The model inputs were drawn simultaneously from probability distributions to produce 10 000 ICERs and the mean, median, and 95% CI.

Role of the Funding Source

This study received no external funding.

RESULTS

Base-Case Analysis

For every 1000 persons, the model predicted that HZ vaccine at age 50 years would prevent 25 cases of HZ and 1 case of PHN over their lifetime, which translates to 0.4 QALY saved at an additional cost of $137 000 (Table 2). If the entire U.S. population of persons aged 50 years in 2013 were vaccinated, 112 652 cases of HZ and 4504 cases of PHN could be avoided over their lifetime. The incremental costs of vaccination versus no vaccination would be almost $613 million, and the ICER would be $323 456 per QALY. Because rates of HZ are higher in women, the ICER would be half as much for women as for men.

Sensitivity Analysis

Scenario Analysis

When vaccination age of 50 to 59 years was considered, cost decreased and effectiveness increased for each year that vaccination was postponed. Thus, vaccination at age 59 years dominated all other ages with the highest effectiveness, the lowest costs, and an ICER of $113 121 per QALY compared with no vaccination (Appendix Figure 3, available at www.annals.org). Providing a booster increased both cost and effectiveness compared with no booster. A booster at age 60 years provided more QALYs at a lower cost than a booster at age 55 years. Compared with no vaccination, vaccination at age 50 years and a booster at age 60 years had an ICER of $174 926 per QALY (Appendix Figure 4, available at www.annals.org). Appendix Table 1 (available at www.annals.org) shows the ICERs of the remaining scenario analyses. If vaccine efficacy were to wane at half the rate seen in the LTPS, the cost of vaccination at age 50 years would decrease to $48 457 per QALY saved. If the efficacy remained constant for 10 years before decreasing, vaccination would be highly attractive (ICER, $14 555 per QALY saved). Other assumptions about HZ incidence and residual efficacy against PHN had less of an effect on the ICER.

Deterministic Sensitivity Analysis

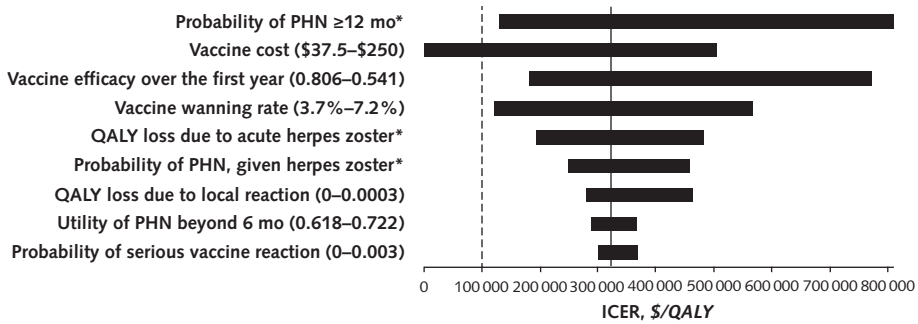
Figure 2 shows the 9 parameters that, when varied through their plausible ranges, caused the ICER to

Table 2. Costs and Effectiveness of HZ Vaccine Versus No Vaccination Among Persons Aged 50 y

Strategy	HZ Cases, *n*	HZ Cases Prevented, *n*	PHN Cases, *n*	PHN Cases Prevented, *n*	Total Cost, $	Incremental Cost, $	QALYs	Incremental QALYs	ICER, *$/QALY*
All									
No vaccination	0.1701	–	0.0175	–	458	–	15.9198	–	–
Vaccine	0.1450	0.0251	0.0165	0.0010	595	137	15.9202	0.0004	323 456
Male									
No vaccination	0.1329	–	0.0135	–	359	–	15.3299	–	–
Vaccine	0.1132	0.0196	0.0127	0.0008	511	152	15.3302	0.0003	487 010
Female									
No vaccination	0.2061	–	0.0214	–	554	–	16.4910	–	–
Vaccine	0.1757	0.0303	0.0202	0.0012	676	122	16.4915	0.0005	230 389

HZ = herpes zoster; ICER = incremental cost-effectiveness ratio; PHN = postherpetic neuralgia; QALY = quality-adjusted life-year.

Figure 2. Tornado diagram of the factors with the most influence on the ICER.



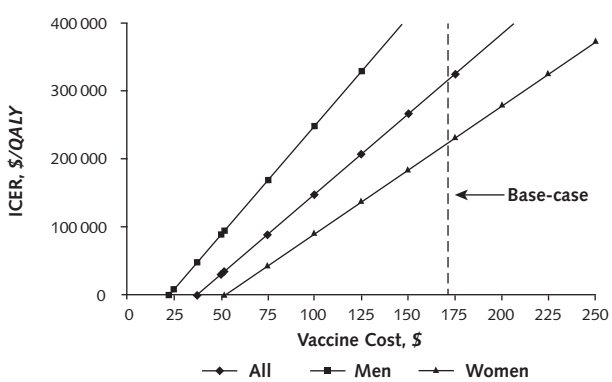
Ranges are in parentheses, with the left values leading to the leftmost ICERs. ICER = incremental cost-effectiveness ratio; PHN = postherpetic neuralgia; QALY = quality-adjusted life-year.
* Ranges for these age-specific parameters are specified in Table 1, with the highest values leading to the leftmost ICERs.

change by more than 10% compared with the base case. Within the plausible ranges, the only variable that produced an ICER less than $100 000 per QALY was vaccine cost (Figure 3). Vaccination had an ICER of $100 000 per QALY at a cost of $80 per dose and an ICER of $50 000 per QALY at a cost of $59 per dose. If vaccination were limited to women, a cost of approximately $78 would result in an ICER of $50 000 per QALY. Among the variables that produced less than a 10% change in the ICER were HZ incidence, probability of ophthalmic complications and herpes oticus, and costs of HZ and complications.

Probabilistic Sensitivity Analysis

In 10 000 iterations of the model with all parameters varied simultaneously, the mean ICER was $500 754 per QALY (95% CI, $93 510 to $1 691 211 per QALY) and the median was $362 123 per QALY. At a willingness-to-pay threshold of $100 000 per QALY, the probability that vaccination would be cost-effective was 3% (Figure 4).

Figure 3. Incremental costs of the herpes zoster vaccine per QALY saved, as a function of vaccine cost and sex.



When cost was <$80 per dose, the incremental costs were <$100 000 per QALY for the whole population. Because women had higher herpes zoster incidence, the incremental costs were <$100 000 per QALY at a higher vaccine cost per dose ($105); the reverse was true for men. ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

DISCUSSION

This cost-effectiveness analysis shows that for 50-year-old adults in the United States, HZ vaccination is likely to offer poor value. Although the vaccine is highly efficacious at that age, the incidence of both HZ and PHN is low, and vaccine efficacy probably decreases to zero over a period of 10 to 12 years (6). Thus, by the age at which HZ incidence increases rapidly, there seems to be no residual effect. At the same time, the cost of vaccination is high. As a result, the ICER was more than $323 000 per QALY. Although the vaccine is more cost-effective in women because they have higher rates of HZ and PHN, the cost-effectiveness in women did not approach accepted thresholds for good value.

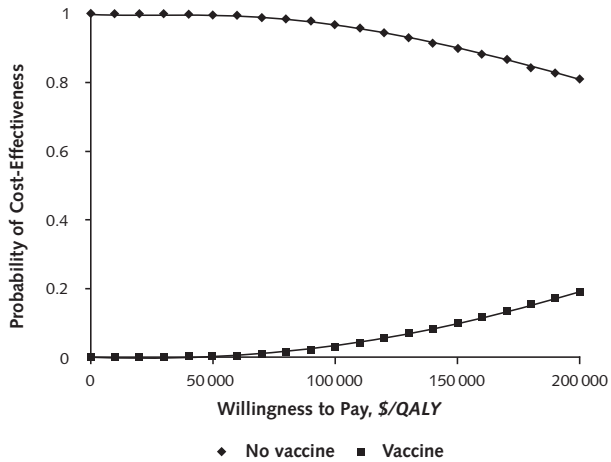
Deterministic and probabilistic sensitivity analyses confirmed the robustness of our findings. Herpes zoster vaccine at age 50 years always had an ICER greater than $100 000 per QALY within the plausible ranges and distributions of model inputs. The ICER was less than $100 000 per QALY only at a vaccine cost less than $80 per dose. We further examined the cost-effectiveness of the vaccine in several scenario analyses and noted several important findings. The cost-effectiveness increased with increasing age at vaccination within the range of 50 to 59 years. However, the vaccine was still expensive even if a patient waited until age 59 years to receive it. Extrapolating the effect of age at vaccination, we believe that waiting until age 60 years, as is currently recommended, would be less expensive and more effective than vaccination at age 59 years. The decreasing rate of vaccine efficacy was another important assumption. The HZ vaccine could be cost-effective even at age 50 years if the efficacy either decreased more slowly than was observed for persons aged 60 years or older or remained stable in the first 10 years after vaccination before decreasing. Further data on long-term vaccine efficacy among persons aged 50 to 59 years would make model estimates more precise.

Finally, although a hypothetical booster dose made the vaccine more cost-effective, the ICER remained high.

Previous models have suggested that the vaccine is most cost-effective among persons aged 70 to 79 years (12, 45–50). However, these studies lacked evidence for the effectiveness of vaccination at age 50 years or the long-term effectiveness of the vaccine, which has only recently been established. By including data from ZEST (9), as well as evidence from the LTPS about duration of immunity (6), we were able to estimate with some certainty the cost-effectiveness of vaccinating younger persons. Two other studies have analyzed the cost-effectiveness of HZ vaccine among persons aged 50 to 59 years in European settings (51, 52). The first study concluded that vaccination was cost-effective at age 50 years or older in the United Kingdom, with an ICER of £13 007 per QALY ($26 196 per QALY in 2014 dollars) under the assumption that vaccine efficacy was lifelong (51). In the second study, conducted in Germany, the authors assumed that efficacy would remain stable for 10 years before decreasing at a rate of 8.3% annually. In that case, vaccination would cost €30 901 per QALY ($40 581 per QALY in 2014 dollars) (52). These assumptions seem unrealistic on the basis of data from the LTPS (6). In the German study, if the efficacy decreased by 8.3% per year after the first year, the ICER would increase to $86 665 per QALY (2014 dollars), and if it decreased by 20% per year (similar to the LTPS), the ICER would be $222 504 per QALY (52), which is similar to our findings. The actual rate of decrease in efficacy for persons aged 50 to 59 years is unknown because ZEST lasted only 1.5 years. The rate of decrease may be slower in younger patients, but it will be at least another 10 years before long-term follow-up data are available (if such data are being collected). A short-term persistence study could also shed light on whether short-term persistence differs in younger patients. If it does, long-term persistence may also differ, and the models would have to be revisited.

Our study has several limitations. First, although we based our analysis on the most current U.S. epidemiologic data, the probability of developing PHN for persons aged 50 to 59 years was based on small studies. In addition, we estimated the probability that PHN will persist beyond 12 months on the basis of data from persons aged 60 to 69 years, which may represent an overestimate for younger patients. If younger patients are at lower risk for prolonged PHN, the vaccine would be more expensive (14). Second, our sex- and age-specific estimates of HZ incidence were based on linear regressions that assumed increasing incidence over time. Although these estimates were not based on observational data for 2010, the regressions allowed us to account for the increasing trend in incidence, and increasing incidence for 5 more years did not change our conclusion. If incidence stopped increasing before 2010, vaccination would be even less cost-effective. Third, our model incorporated data on initial vaccine efficacy from ZEST. Because the vaccine requires special handling (it must be stored frozen, then thawed, reconstituted, and injected within 30 minutes), effectiveness in clinical practice may be lower than we estimated. At least 1 large observational study suggests that effectiveness in younger patients may be decreased by as much as one third compared with randomized trials (53). In that case, vaccination would be even less cost-effective. Finally, some estimates of costs associated with HZ and PHN are outdated. We possessed recent estimates of productivity loss, but many estimates of health-related costs were based on studies from the 1990s updated to 2014 dollars. Contemporary estimates are needed. However, because HZ and PHN were rare in this age group, even wide variation of these costs in sensitivity analysis did not substantially change the ICER.

Figure 4. Cost-effectiveness acceptability curve for the herpes zoster vaccine versus no vaccination at age 50 y.



QALY = quality-adjusted life-year.

In conclusion, vaccination at age 50 years should improve health outcomes but, on the basis of available information, does not represent good value according to generally accepted standards. Our findings were robust to wide variations in all model inputs. Reducing the vaccine cost could produce an ICER below $100 000 per QALY, but only at a price far below what is currently charged. At current prices, affluent patients might still choose to be vaccinated before age 60 years, but congruent with the recommendation of the Advisory Committee on Immunization Practices, our cost-effectiveness results do not support universal vaccination for this age group.

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Appendix: Additional Model Details

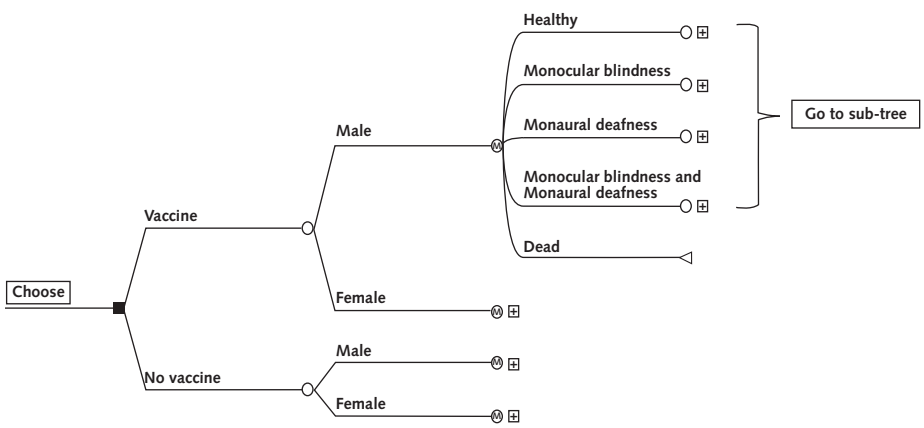
Model Choice for Increase in HZ Incidence

We modeled the increase in age- and sex-specific HZ incidence over time based on data from 1993 to 2006 reported by Leung and colleagues (13). We tested the data against exponential, linear, and logarithmic regression models in Excel 2010 (Microsoft). Linear regression models generally provided the best fit as measured by the R^2 values (Appendix Table 2). We created 6 separate age- and sex-specific models based on the point estimates. For simplicity, we did not consider the uncertainty around those estimates. Specific linear regression characteristics of age- and sex-specific HZ incidence are provided in Appendix Tables 3 to 8.

Modeling the Decrease in HZ Vaccine Efficacy

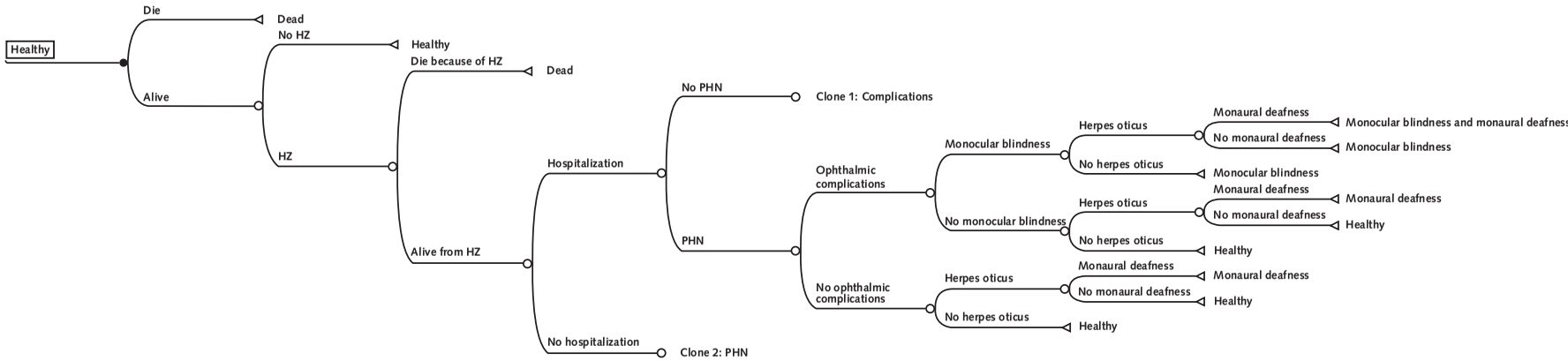
ZEST reported the vaccine efficacy among persons aged 50 to 59 years up to 1.5 years after vaccination (8). Because long-term efficacy data are not available for this age group, we used the data reported in the LTPS to estimate a function for decreasing vaccine efficacy (5). We took 6 efficacy data points corresponding to the first 6 years after vaccination. Because the LTPS had relatively few participants in the last 4 years compared with previous years, we estimated a single efficacy based on the weighted average follow-up time in the LTPS (year 7.7 after vaccination). We tested these 7 data points against different regression models, including linear, exponential, and logarithmic ones. The linear regression model offered the best fit as judged by the R^2 value. In the base case, we used the point estimates but considered 95% CIs for deterministic and probabilistic sensitivity analyses. Finally, to arrive at the efficacy function for persons aged 50 to 59 years, the intercept of the efficacy function was adjusted upward so that the efficacy 1 year after vaccination estimated by the function was equal to the estimate reported in ZEST. The specific regression characteristics of the decreasing efficacy function based on the LTPS are provided in Appendix Tables 9 and 10.

Appendix Figure 1. Markov model: decision node and Markov states.



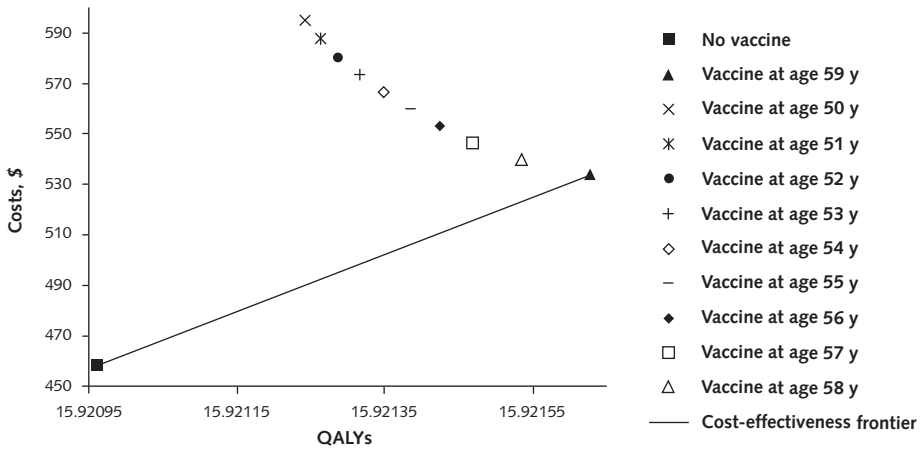
The model begins with a decision node representing the choice between the vaccine or no vaccination. The cohort then moves to a chance node (*open circle*) of male or female, depending on the sex distribution of the general population, and then enters the Markov node (*letter "M" inside circle*). For the first cycle, the entire cohort enters the "healthy" state, then moves between Markov health states depending on transition probabilities in subsequent cycles until everyone is subsumed by the "dead" state, at which point the model terminates.

Appendix Figure 2. Markov model: sub-tree.



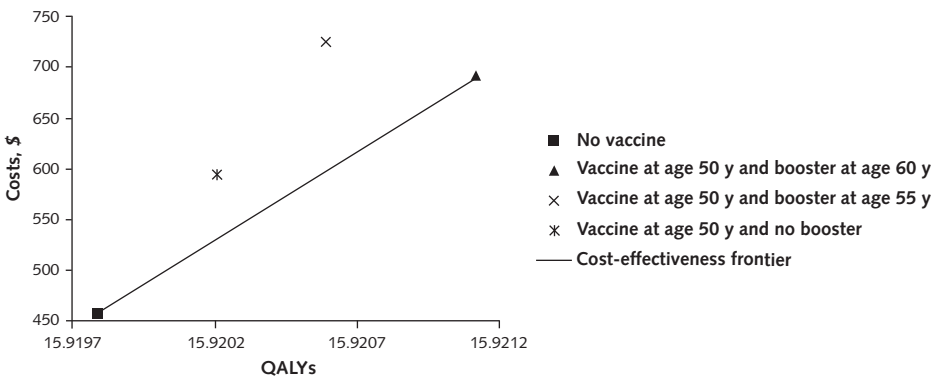
The chance of events occurring within each annual cycle for persons starting at the "healthy" state. For subsequent cycles beginning in the "monocular blindness," "monaural deafness," or "monocular blindness and monaural deafness" states, the tree is identical, but cohort members return to the corresponding initial states instead of "healthy" after recovering from HZ and any short-term complications (hospitalization and PHN). Those who acquire a second disability move to the combined disability state. Bilateral blindness and deafness are extremely rare and are not considered. HZ = herpes zoster; PHN = postherpetic neuralgia.

Appendix Figure 3. Costs versus QALYs for different vaccination ages.



Vaccination at age 59 y, which had the lowest costs and highest QALYs, dominated vaccination at all other ages. The slope of the line between the "no vaccine" and "vaccine at age 59 y" points represents the incremental cost per QALY saved ($113 121) when the 2 strategies were compared. QALY = quality-adjusted life-year.

Appendix Figure 4. Costs versus QALYs for different booster strategies.



The "vaccine at age 50 y and booster at age 55 y" strategy was dominated because it had a higher cost and lower QALYs than the "vaccine at age 50 y and booster at age 60 y" strategy. The "vaccine at age 50 y and no booster" strategy was not considered for comparison due to extended dominance; it had a higher incremental cost per QALY (ICER) than the next more effective strategy, which was "vaccine at age 50 y and booster at age 60 y." The slope of the line between the "no vaccine" and "vaccine at age 50 y and booster at age 60 y" points represents the ICER of $174 926 per QALY when the 2 strategies were compared. ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Appendix Table 1. Scenario Analysis

Scenario	Costs, $		QALYs		Incremental Costs, $	Incremental QALYs	ICER, $/QALY
	No Vaccine	Vaccine	No Vaccine	Vaccine			
HZ incidence increased for 5 more years after 2010, then plateaued	522	652	15.9182	15.9187	130	0.0005	279 596
Rate of decrease in vaccine efficacy was half that in the base case (−0.0272)	458	524	15.9198	15.9211	66	0.0014	48 457
Vaccine efficacy was constant in the first 10 y, then decreased at age 60 y	458	482	15.9198	15.9214	24	0.0017	14 555
Vaccine had additional effect on PHN beyond effect on incidence	458	595	15.9198	15.9203	136	0.0005	276 072

HZ = herpes zoster; ICER = incremental cost-effectiveness ratio; PHN = postherpetic neuralgia; QALY = quality-adjusted life-year.

Appendix Table 2. R^2 Values of Different Regression Model Types for Age- and Sex-Specific Herpes Zoster Incidence

Population	R^2 Value		
	Exponential	Logarithmic	Linear
Men			
Aged 50–59 y	0.93	0.95	0.95
Aged 60–69 y	0.90	0.87	0.91
Aged ≥70 y	0.92	0.86	0.92
Women			
Aged 50–59 y	0.95	0.89	0.97
Aged 60–69 y	0.95	0.78	0.94
Aged ≥70 y	0.84	0.88	0.91

Appendix Table 3. Specifications of the Linear Regression Model for Herpes Zoster Incidence Among Men Aged 50 to 59 y

Regression Statistics	
Multiple R	0.9752
R^2	0.9511
Adjusted R^2	0.9470
Standard error	0.1038
Observations	14

ANOVA

	df	SS	MS	*F* Value	Significance *F* Value
Regression	1	2.5108	2.5108	233.2263	3.16453E-09
Residual	12	0.1292	0.0108		
Total	13	2.6400			

	Coefficient	Standard Error	*t* Statistic	*P* Value	Lower 95% Confidence Limit	Upper 95% Confidence Limit
Intercept	−207.3574	13.7547	−15.0754	0.0000	−237.3262	−177.3885
X variable 1	0.1051	0.0069	15.2717	0.0000	0.0901	0.1200

ANOVA = analysis of variance; df = degrees of freedom; MS = mean square; SS = sum of squares.

Appendix Table 4. Specifications of the Linear Regression Model for Herpes Zoster Incidence Among Men Aged 60 to 69 y

Regression Statistics	
Multiple R	0.9541
R^2	0.9104
Adjusted R^2	0.9029
Standard error	0.2219
Observations	14

ANOVA

	df	SS	MS	*F* Value	Significance *F* Value
Regression	1	6.0013	6.0013	121.8929	1.21684E-07
Residual	12	0.5908	0.0492		
Total	13	6.5921			

	Coefficient	Standard Error	*t* Statistic	*P* Value	Lower 95% Confidence Limit	Upper 95% Confidence Limit
Intercept	−320.1897	29.4148	−10.8853	0.0000	−384.2790	−256.1003
X variable 1	0.1624	0.0147	11.0405	0.0000	0.1304	0.1945

ANOVA = analysis of variance; df = degrees of freedom; MS = mean square; SS = sum of squares.

Appendix Table 5. Specifications of the Linear Regression Model for Herpes Zoster Incidence Among Men Aged ≥70 y

Regression Statistics	
Multiple R	0.9615
R^2	0.9245
Adjusted R^2	0.9182
Standard error	0.3500
Observations	14

ANOVA

	df	SS	MS	*F* Value	Significance *F* Value
Regression	1	18.0044	18.0044	146.9856	4.31312E-08
Residual	12	1.4699	0.1225		
Total	13	19.4743			

	Coefficient	Standard Error	*t* Statistic	*P* Value	Lower 95% Confidence Limit	Upper 95% Confidence Limit
Intercept	−555.5396	46.3963	−11.9738	0.000	−656.6284	−454.4507
X variable 1	0.2813	0.0232	12.1238	0.000	0.2308	0.3319

ANOVA = analysis of variance; df = degrees of freedom; MS = mean square; SS = sum of squares.

Appendix Table 6. Specifications of the Linear Regression Model for Herpes Zoster Incidence Among Women Aged 50 to 59 y

Regression Statistics	
Multiple R	0.9840
R^2	0.9683
Adjusted R^2	0.9657
Standard error	0.1565
Observations	14

ANOVA

	df	SS	MS	*F* Value	Significance *F* Value
Regression	1	8.9804	8.9804	366.6838	2.32E-10
Residual	12	0.2939	0.0245		
Total	13	9.2742			

	Coefficient	Standard Error	*t* Statistic	*P* Value	Lower 95% Confidence Limit	Upper 95% Confidence Limit
Intercept	−393.2062	20.7460	−18.9534	0.0000	−438.4077	−348.0046
X variable 1	0.1987	0.0104	19.1490	0.0000	0.1761	0.2213

ANOVA = analysis of variance; df = degrees of freedom; MS = mean square; SS = sum of squares.

Appendix Table 7. Specifications of the Linear Regression Model for Herpes Zoster Incidence Among Women Aged 60 to 69 y

Regression Statistics	
Multiple R	0.9695
R^2	0.9399
Adjusted R^2	0.9349
Standard error	0.2880
Observations	14

ANOVA

	df	SS	MS	*F* Value	Significance *F* Value
Regression	1	15.5615	15.5615	187.5629	1.09502E-08
Residual	12	0.9956	0.0830		
Total	13	16.5571			

	Coefficient	Standard Error	*t* Statistic	*P* Value	Lower 95% Confidence Limit	Upper 95% Confidence Limit
Intercept	−516.6319	38.1843	−13.5300	0.0000	−599.8282	−433.4355
X variable 1	0.2615	0.0191	13.6954	0.0000	0.2199	0.3031

ANOVA = analysis of variance; df = degrees of freedom; MS = mean square; SS = sum of squares.

Appendix Table 8. Specifications of the Linear Regression Model for Herpes Zoster Incidence Among Women Aged ≥70 y

Regression Statistics	
Multiple R	0.9542
R^2	0.9104
Adjusted R^2	0.9030
Standard error	0.6589
Observations	14

ANOVA

	df	SS	MS	*F* Value	Significance *F* Value
Regression	1	52.9453	52.9453	121.9547	1.21345E-07
Residual	12	5.2097	0.4341		
Total	13	58.1550			

	Coefficient	Standard Error	*t* Statistic	*P* Value	Lower 95% Confidence Limit	Upper 95% Confidence Limit
Intercept	−956.4440	87.3466	−10.9500	0.0000	−1146.756	−766.1320
X variable 1	0.4824	0.0437	11.0433	0.0000	0.3872	0.5776

ANOVA = analysis of variance; df = degrees of freedom; MS = mean square; SS = sum of squares.

Appendix Table 9. Equations and R^2 Values of Different Regressions of Herpes Zoster Efficacy

Regression Type	Regression Equation	R^2 Value
Exponential	$y = 0.7306 \times e^{-0.144x}$	0.9018
Logarithmic	$y = 0.174 \times \ln(x) + 0.6387$	0.8577
Linear	$y = 0.6478 - 0.0544x$	0.9165

Appendix Table 10. Specifications of the Linear Regression Model for Herpes Zoster Vaccine Efficacy

Regression Statistics	
Multiple R	0.9646
R^2	0.9304
Adjusted R^2	0.9165
Standard error	0.0382
Observations	7

ANOVA

	df	SS	MS	*F* Value	Significance *F* Value
Regression	1	0.0975	0.0975	66.8297	0.00044531
Residual	5	0.0073	0.0015		
Total	6	0.1048			

	Coefficient	Standard Error	*t* Statistic	*P* Value	Lower 95% Confidence Limit	Upper 95% Confidence Limit
Intercept	0.6478	0.0309	20.9510	0.0000	0.5683	0.7273
X variable 1	−0.0544	0.0067	−8.1749	0.0004	−0.0716	−0.0373

ANOVA = analysis of variance; df = degrees of freedom; MS = mean square; SS = sum of squares.