

Cost-Effectiveness of a Vaccine To Prevent Herpes Zoster and Postherpetic Neuralgia in Older Adults

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Background: The Shingles Prevention Study showed that a varicella-zoster virus (VZV) vaccine administered to adults 60 years of age or older reduced the incidence of herpes zoster from 11.12 to 5.42 cases per 1000 person-years. Median follow-up was 3.1 years, and relative risk reduction was 51.3% (95% CI, 44.2% to 57.6%).

Objective: To assess the extent to which clinical and cost variables influence the cost-effectiveness of VZV vaccination for preventing herpes zoster in immunocompetent older adults.

Design: Decision theoretical model.

Data Sources: English-language data published to March 2006 identified from MEDLINE on herpes zoster rates, vaccine effectiveness, quality of life, medical resource use, and unit costs.

Target Population: Immunocompetent adults 60 years of age or older with a history of VZV infection.

Time Horizon: Lifetime.

Perspective: U.S. societal.

Interventions: Varicella-zoster virus vaccination versus no vaccination.

Outcome Measures: Incremental quality-adjusted survival and cost per quality-adjusted life-year (QALY) gained.

Results of Base-Case Analysis: By reducing incidence and severity of herpes zoster, vaccination can increase quality-adjusted survival

by 0.6 day compared with no vaccination. One scenario in which vaccination costs less than \$100 000 per QALY gained is when 1) the unit cost of vaccination is less than \$200, 2) the age at vaccination is less than 70 years, and 3) the duration of vaccine efficacy is more than 30 years.

Results of Sensitivity Analysis: Vaccination would be more cost-effective in “younger” older adults (age 60 to 64 years) than in “older” older adults (age \geq 80 years). Longer life expectancy and a higher level of vaccine efficacy offset a lower risk for herpes zoster in the younger group. Other factors influencing cost-effectiveness include quality-of-life adjustments for acute zoster, unit cost of the vaccine, risk for herpes zoster, and duration of vaccine efficacy.

Limitations: The effectiveness of VZV vaccination remains uncertain beyond the median 3.1-year duration of follow-up in the Shingles Prevention Study.

Conclusions: Varicella-zoster virus vaccination to prevent herpes zoster in older adults would increase QALYs compared with no vaccination. Resolution of uncertainties about the average quality-of-life effects of acute zoster and the duration of vaccine efficacy is needed to better determine the cost-effectiveness of zoster vaccination in older adults.

Ann Intern Med. 2006;145:317-325.

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Herpes zoster results from reactivation of latent varicella-zoster virus (VZV) infection residing in sensory ganglia. The disease presents as a clinical syndrome characterized by a painful vesicular eruption (1). In the United States, herpes zoster affects about 300 000 to 600 000 persons annually (2). Sequelae occur in about 12% of cases and include postherpetic neuralgia (PHN) (7.9%), bacterial skin infections (2.3%), ocular complications (such as uveitis and keratitis) (1.6%), motor neuropathy (0.9%), meningitis (0.5%), and herpes simplex virus oticus (0.2%) (3). Herpes zoster incidence is approximately 2.2 cases per 1000 person-years and peaks at 14.2 cases per 1000 person-years for individuals older than age 75 years (4, 5).

The Shingles Prevention Study examined whether vaccination with a live attenuated VZV vaccine would decrease the incidence and severity of herpes zoster and PHN in adults 60 years of age or older (6). Vaccination statistically significantly reduced the incidence of zoster from 11.12 to 5.42 cases per 1000 person-years. Median follow-up was 3.1 years, and relative risk reduction was 51.3% (95% CI, 44.2% to 57.6%). The incidence of PHN at 90 days was reduced from 1.38 cases to 0.46 case

per 1000 person-years, and relative risk reduction was 66.5% (CI, 47.5% to 79.2%).

The published price for the pediatric VZV vaccine (Varivax, Merck & Co., Whitehouse Station, New Jersey) is \$56.90 for the Centers for Disease Control and Prevention (CDC) and \$66.81 for the private sector (7). In an editorial accompanying the Shingles Prevention Study report, Gilden (8) suggested that a price of \$500 for the adult vaccine would probably be cost-effective and would

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Context

A recent large trial proved that a live attenuated varicella-zoster virus vaccine reduced the incidence and severity of herpes zoster in older adults.

Contribution

This decision model suggests that vaccination could improve quality-adjusted survival by small amounts. Vaccination is, however, unlikely to cost less than \$100 000 per quality-adjusted life year gained unless the vaccination cost is less than \$200 and duration of vaccine efficacy exceeds 20 years. Targeting adults 60 to 69 years of age rather than those older than 80 years of age would be most cost-effective.

Cautions

We do not yet know how long the vaccine remains effective.

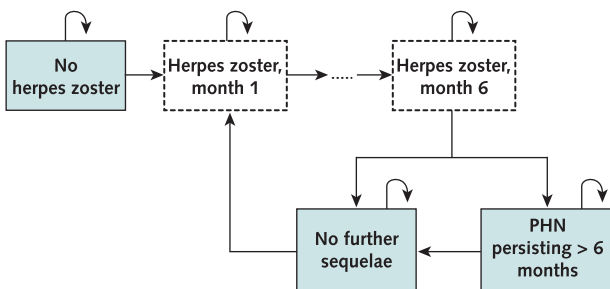
—The Editors

perhaps even be cost-saving. Even at a cost of \$56.90 for the vaccine, the estimated U.S. expenditures for the vaccine could exceed \$2.8 billion if routine vaccination were recommended for all adults 60 years of age or older (more than 49 million people in 2005). Policy decisions about such a large public expenditure should be based on further assessment of the program’s clinical and economic implications. We performed an analysis of the cost-effectiveness of VZV vaccination in immunocompetent older adults.

METHODS

We constructed a decision theoretical model with Microsoft Office Excel 2003 and Microsoft Visual Basic 6.3 software (Microsoft Corp., Redmond, Washington) to compare the clinical and economic effects of VZV vaccination with those of no vaccination in older adults (Figure 1). At a given time, a patient may be in one of a finite

Figure 1. Markov state transition model.



A patient occupies a tunnel state (white boxes) for 1 cycle only. Curved arrows denote death. The effect of herpes zoster on burden of illness in the model reflects the findings of the Shingles Prevention Study (6). PHN = postherpetic neuralgia.

number of health states. Events are modeled as transitions from one state to another. For each state, a utility is assigned as an adjustment factor for quality of life. Utility weights typically range from 0 to 1, in which 0 represents a state as bad as death, 1 represents perfect health, and values between 0 and 1 represent states between these extremes. The contribution to total utility, commonly called quality-adjusted life-years (QALYs), of a particular state consists of the length of time spent in a state multiplied by the utility of that state.

The target population is immunocompetent persons 60 years of age or older (median age, 69 years) with a history of VZV infection (6). The representative person starts without herpes zoster but may later experience clinical herpes zoster (6). Six months after onset of acute zoster—the duration of follow-up of a zoster episode in the Shingles Prevention Study—the patient may experience persistent PHN (9) or have no zoster-related sequelae. Risk for a subsequent case of herpes zoster is equal to that of the first event (4, 10–14).

Data Sources

We conducted searches of English-language literature published from 1966 to March 2006 by using PubMed. We specifically looked for original-data studies that provided descriptive statistics pertinent to the following questions: What is the duration of PHN? What is the duration of vaccine efficacy? What is the lost work productivity due to an episode of acute zoster? What are the costs of an acute zoster episode and PHN? The Appendix (available at www.annals.org) provides details of these searches.

Data and Assumptions

The model captures 3 effects of vaccination: 1) incidence of herpes zoster, 2) zoster-specific burden of illness, and 3) incidence and duration of PHN among patients with herpes zoster (Table 1).

The Shingles Prevention Study (6) provided data on the age-related incidence of herpes zoster. The number of persons needed to vaccinate to prevent 1 herpes zoster episode over the 3.1 years of the Shingles Prevention Study varied from 46 persons 65 to 69 years of age to 152 persons 85 to 89 years of age.

Investigators of the Shingles Prevention Study selected the participant’s burden of illness as the protocol-specified primary end point. They obtained burden-of-illness scores from patient responses to the “worst pain” question of the Zoster Brief Pain Inventory (9). Responses could range from “no pain” (score of 0) to “pain as bad as you can imagine” (score of 10). Analysts computed the burden-of-illness score as the area under the curve of pain scores reported over the 182 days of follow-up from onset of herpes zoster (score range, 0 to 1813). They assigned a score of 0 to participants who never experienced herpes zoster and defined PHN as a burden-of-illness score of 3 or higher occurring after 90 days from the onset of a zoster rash. The mean burden-of-illness score for participants

Table 1. Model Assumptions*

Variables	Value of Inputs: Base Case (5th to 95th Percentile)†		Source‡
	Vaccine	No Vaccine	
Incidence of herpes zoster per 1000 person-years over 3 y by age group			FDA briefing document of the Shingles Prevention Study (Rohan, 2005 [15])
Age 60–64 y	3.44 (2.59 to 4.49)	9.95 (8.43 to 11.65)	
Age 65–69 y	4.35 (3.38 to 5.52)	11.63 (10.00 to 13.45)	
Age 70–74 y	6.44 (5.17 to 7.92)	11.44 (9.72 to 13.37)	
Age 75–79 y	7.18 (5.57 to 9.12)	11.31 (9.23 to 13.73)	
Age 80–84 y	9.77 (6.65 to 13.87)	12.23 (8.70 to 16.72)	
Age 85–89 y	10.04 (3.26 to 23.43)	11.57 (4.65 to 23.84)	
Age ≥ 90 y§	12.40 (0.50 to 109.25)	14.29 (0.36 to 79.59)	
Burden-of-illness scores for case of herpes zoster (range, 0–1813)	147.1 (126.0 to 168.2)	177.7 (157.9 to 197.4)	FDA briefing document of the Shingles Prevention Study (Rohan, 2005 [15])
Probability of persistent PHN at 182 d after onset of zoster episode, %	2.9 (1.3 to 5.4)	5.1 (3.6 to 7.1)	Shingles Prevention Study (Oxman et al., 2005 [6])
Duration of persistent PHN from start of zoster episode, mo	8 (0 to 18)	8 (0 to 18)	Estimated from the Shingles Prevention Study (Oxman et al., 2005 [6])
Risk for zoster-related death per 10 000 persons by age group			Edmunds et al., 2001 (16)
Age 60–64 y	0 (0 to 0)	0 (0 to 0)	
Age 65–69 y	0.25 (0 to 0.5)	0.25 (0 to 0.5)	
Age 70–74 y	0.75 (0.5 to 1.0)	0.75 (0.5 to 1.0)	
Age 75–79 y	2.5 (0 to 4)	2.5 (0 to 4)	
Age 80–84 y	9.5 (0 to 15)	9.5 (0 to 15)	
Age ≥ 85 y	28 (0 to 38)	28 (0 to 38)	
Probability of vaccine injection site reaction, %	31.7 (28.3 to 32.6)	NA	Oxman et al., 2005 (6)
Duration of vaccine injection site reaction, d	2 (0 to 5)	NA	Assumption
Duration of vaccine efficacy, y	30 (3 to 30)	NA	Assumption
Utilities			
No zoster or no sequelae	0.860 (0.740 to 0.980)	0.860 (0.740 to 0.980)	Coplan et al., 2004 (9)
Acute zoster (from 1 to 182 d)	0.822 (0.702 to 0.942)	0.811 (0.691 to 0.931)	
PHN	0.594 (0.474 to 0.714)	0.594 (0.474 to 0.714)	
Vaccine site reaction	0.900 (0.810 to 0.990)	NA	Assumption
Direct medical costs for management of herpes zoster			
Outpatient visits, \$	112 (56 to 224)	112 (56 to 224)	CMS prevailing cost for 2 office visits (17)
Antiviral treatment costs, \$	180 (135 to 288)	180 (135 to 288)	AWP (18–20); retail prices (21, 22)
Probability of hospitalization, %	1.15 (0 to 3)	1.15 (0 to 3)	Shingles Prevention Study (Oxman et al., 2005 [6])
Cost per hospitalization, \$	6884 (3982 to 7935)	6884 (3982 to 7935)	CMS (23, 24); Lin and Hadler, 2000 (25)
PHN costs per month, \$	166 (53 to 351)	166 (53 to 351)	Smith and Roberts, 2000 (26)
Total costs, \$			
Vaccinated	576 (256 to 1263)	576 (256 to 1263)	
Unvaccinated¶	606 (266 to 1327)	606 (266 to 1327)	
Indirect costs (lost labor) by age group, \$**			Bureau of Labor Statistics, 2006 (27)
Age 60–64 y	1934 (0 to 3868)	1934 (0 to 3868)	
Age 65–69 y	744 (0 to 1488)	744 (0 to 1488)	
Age 70–74 y	439 (0 to 878)	439 (0 to 878)	
Age ≥ 75 y	185 (0 to 370)	185 (0 to 370)	
Vaccination costs, \$††	Variable (50 to 500)	Variable (50 to 500)	CDC, 2006 (7); Gilden, 2005 (8)

* AWP = average wholesale price; CDC = Centers for Disease Control and Prevention; CMS = Centers for Medicare & Medicaid Services; FDA = U.S. Food and Drug Administration; NA = not applicable; PHN = postherpetic neuralgia.

† Fifth and 95th percentiles were used for ranges in sensitivity analyses. Costs are in 2006 U.S. dollars.

‡ Numbers in parentheses and square brackets are references.

§ Forty-four participants were ≥90 years of age, providing an insufficient sample to estimate the effect of vaccine in this age cohort. We assumed, therefore, that the zoster incidence was lowered in the same proportion for this age cohort as for the participants 85 to 89 years of age.

|| The point estimate is based on the Shingles Prevention Study (Oxman et al., 2005 [6]), and the range is from Edmunds et al., 2001 (16).

¶ Total direct medical costs are higher for unvaccinated patients than for vaccinated patients because of the higher percentage of cases that result in persistent PHN (2.9% vaccinated vs. 5.1% unvaccinated).

** Computed as the product of percentage of labor participation and mean weekly wage. See Appendix Table 5, available at www.annals.org.

†† Includes unit vaccine cost, public awareness campaign, administration costs, patient travel time and time receiving vaccine, and cost of treating adverse events.

Table 2. Results

Variable*	Base Case (Age 69 Years)			Age 60 Years			Age 65 Years			Age 70 Years		
	Vaccine	No Vaccine	Difference	Vaccine	No Vaccine	Difference	Vaccine	No Vaccine	Difference	Vaccine	No Vaccine	Difference
Cumulative incidence of zoster cases, %	11.8	17.8	-6.0†	12.3	23.2	-10.7†	12.4	20.6	-8.3†	11.7	17.0	-5.3†
Cumulative lifetime duration of zoster cases, y	0.058	0.088	-0.029	0.062	0.116	-0.053	0.061	0.102	-0.041	0.058	0.084	-0.026
Quality-adjusted life-years	9.9111	9.9095	0.0016	12.7929	12.7905	0.0024	11.2499	11.2478	0.0020	9.5700	9.5685	0.0015
Costs, \$												
Direct medical care of zoster episode‡	61	98	-37	63	126	-63	63	113	-50	61	94	-33
Lost work productivity	29	49	-20	65	158	-94	38	76	-38	27	42	-15

* Cumulative was defined as total over time horizon.

† Values are percentage points.

‡ Excludes vaccination costs.

who had herpes zoster was 147.1 for vaccinated patients and 177.7 for unvaccinated patients (15).

Among the 315 vaccinated persons who developed acute zoster, 27 (8.6%) cases of PHN occurred, and 9 (2.9%) of these cases lasted longer than 6 months. Among the 642 unvaccinated persons who developed acute zoster, 80 (12.5%) cases of PHN occurred, and 33 (5.1%) of these cases lasted longer than 6 months. The daily resolution rate varied between 0.63% and 1.48%, with no reported difference between study groups. We assumed an average daily rate of resolution for both groups of 1.1%. At this rate, more than half of patients would resolve PHN by 8 months after the onset of acute zoster (range, 6 to 18 months).

The probability of death in the Shingles Prevention Study was 0.013% and did not differ between the vaccinated and unvaccinated study groups (6). We assumed that the risk for zoster-related death increased with age, as reported elsewhere (16). We also considered the age- and sex-specific risk for death from other conditions in the model.

Vaccine-related injection site reactions occurred in 31.7% of patients (range, 28.3% to 32.6%), consisting of erythema (28.8%), pain or tenderness (26%), swelling (21.7%), pruritus (6.1%), warmth (1.4%), hematoma (0.2%), or rash (0.2%) (6). We assumed that the average duration of symptoms was 2 days (range, 0 to 5 days).

The duration of vaccine efficacy beyond the median 3.1-year duration of follow-up in the Shingles Prevention Study is unknown. On the basis of Japanese and U.S. studies, the CDC reports that protection for children lasts for at least 15 to 25 years with the childhood VZV vaccine (28). However, the CDC cautions that protection is never

known when a vaccine is first introduced, and surveillance studies of the childhood vaccine that assess the durability of efficacy are ongoing. Given this uncertainty, we estimated the cost-effectiveness of adult VZV vaccination for durations of efficacy ranging from 3 to 30 years.

Utilities

We assigned utilities to the health states in the model: no zoster, acute zoster, and PHN. A paper by the investigators of the Shingles Prevention Study estimated utilities by using the EuroQoL visual analogue scale (VAS) scores (9). At baseline in the Shingles Prevention Study, the utility for no herpes zoster was 0.860. Among participants with PHN, the mean utility was 0.594. We applied a range of utilities in sensitivity analyses.

We computed QALYs as the sum of mean discounted durations of health states weighted by the utility for each health state. We calculated incremental cost-effectiveness ratios as the difference in discounted costs between vaccination and no vaccination (incremental costs per herpes zoster case avoided) divided by the difference in benefits (QALYs gained).

Costs

We collected costs from various published sources. Smith and Roberts (26) provided a detailed synthesis of 5 studies on the costs (in 1995 U.S. dollars) of managing herpes zoster in immunocompetent persons. We replicated their study method by using the same cost categories, but we updated inputs by using contemporary data sources.

We included costs of 2 physician office visits for an established patient (Current Procedural Terminology [CPT] 99213) (17). Antivirals for herpes zoster include acyclovir, 800 mg, taken orally 5 times daily for 7 days;

Table 2—Continued

Age 75 Years			Age 80 Years		
Vaccine	No Vaccine	Difference	Vaccine	No Vaccine	Difference
10.2	13.6	-3.5†	8.7	10.8	-2.0†
0.050	0.067	-0.017	0.043	0.053	-0.010
7.8660	7.8650	0.0011	6.2252	6.2245	0.0007
54	77	-23	47	62	-14
17	23	-6	15	19	-4

famciclovir, 750 mg, taken orally once daily for 7 days; and valacyclovir, 1000 mg, taken orally 3 times daily for 7 days. We used average wholesale prices published in *Mosby's Drug Consult 2006* (18–20) and retail prices from 2 online retailers (21, 22).

The Shingles Prevention Study reported a 1.15% risk for zoster-related hospitalization (6). We obtained reimbursement for zoster-related hospitalizations from the Medicare Provider Analysis and Review (MEDPAR) inpatient hospital national data from the Centers for Medicare & Medicaid Services (CMS) (29). Files contained data on discharges and reimbursements associated with the following hospitalizations: central nervous system (International Classification of Diseases, Ninth Revision [ICD-9] code 530; diagnosis-related group [DRG] 21; 2231 discharges; reimbursements, \$17 703 552); ophthalmologic (ICD-9 code 5322; DRG 46; 3889 discharges; reimbursements, \$15 284 827); otitis (ICD-9 code 5371; DRG 73; 8044 discharges; reimbursements, \$32 034 603); and nervous system, not otherwise specified (ICD-9 code 5310; DRG 18; 33 657 discharges; reimbursements, \$169 134 975). The average cost for these 4 types of hospitalization, adjusted to 2006 U.S. dollars, was \$6884. We estimated the sum of all costs for an episode of zoster (in 2006 U.S. dollars) to be \$576 (range, \$90 to \$1061) if vaccinated and \$538 (range, \$84 to \$991) if unvaccinated.

We computed indirect cost of lost labor participation by using information from the U.S. Department of Labor Bureau of Labor Statistics (27, 30). In 2002, a reported median of 15 days of work was missed because of acute zoster (30). Among persons 60 to 65 years of age, labor participation was 58% for men and 46% for women. Among persons 75 years of age or older, the labor participation rate decreased to 9% for men and 5% for women. Mean weekly wage was \$847 for men and \$616 for women

55 to 65 years of age, decreasing to \$580 for men and \$434 for women older than 65 years of age (27). Assuming that workers with zoster miss 15 days of work, the mean cost of lost labor participation for persons 65 to 69 years of age is \$744.

The childhood VZV vaccine costs between \$50 and \$100 (vaccine cost plus facility fee) (8). The cost for the adult VZV vaccine is reported to be potentially cost-effective at a unit cost of \$500 (8). We therefore analyzed the vaccine's cost-effectiveness over a cost range of \$50 to \$500, which includes unit vaccine cost, a public awareness campaign, administration costs, patient travel time and time receiving vaccine, and the cost of treating adverse events.

We found the boost in cell-mediated immunity to VZV to extend beyond 24 months, but its long-term durability is not yet fully determined (15). We analyzed the vaccine's cost-effectiveness over the duration of efficacy range of 3 to 30 years.

Model Perspective and Policy Assumptions

We conducted the analysis from a societal perspective over the lifetime of a patient. Cycle length was monthly, and we discounted all costs and benefits at a fixed annual rate of 3% (31).

Sensitivity Analyses

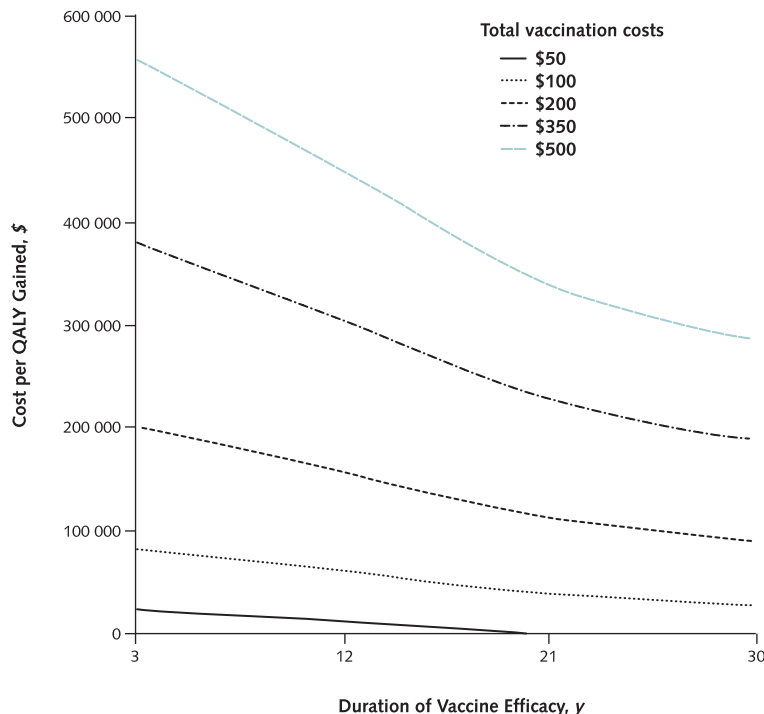
We explored the range of cost-effectiveness by varying each input variable individually. For these analyses, we set the duration of vaccine efficacy to 30 years and the vaccine cost at \$200. We also estimated the probability that the cost-effectiveness ratio was less than \$50 000 and \$100 000 when simultaneously changing all variables by using probabilistic analysis. We assigned each variable in the model a distribution on the basis of values in the literature or expert opinion. We then randomly sampled the distributions of all variables, and we applied the sample inputs to compute a unique estimate of cost per QALY. We repeated sampling to generate descriptive statistics on the cost per QALY gained with vaccination.

Critique of Data Quality

We obtained evidence on herpes zoster incidence and its effect on burden of illness from one of the largest randomized, controlled trials conducted in the past decade, which enrolled almost 40 000 participants. The trial also provided evidence on the effectiveness of vaccination up to a median follow-up of 3.1 years. Until longer follow-up data are available, the assumption of the duration of vaccine efficacy must be based on other data sources. We used data on the related vaccine for childhood immunization against VZV. The Shingles Prevention Study provided data on the participants who had persistent PHN at 6 months after onset of herpes zoster. We used data from the trial to determine the rate of resolution and, thereby, the mean duration of PHN.

We retrieved information on treatment patterns and cost of managing herpes zoster from published sources. We

Figure 2. Cost per quality-adjusted life-year (QALY) gained as a function of duration of vaccine efficacy (from 3 to 30 years) and total vaccination costs (from \$50 to \$500).



Total vaccination costs, \$	3	12	21	30
500	558 750	451 875	340 625	285 625
350	380 625	305 625	228 125	189 375
200	201 875	159 375	115 000	93 125
100	83 125	61 875	40 000	28 750
50	23 750	13 125	1 875	Cost-saving

Total vaccination costs include unit vaccine cost, a public awareness campaign, administration costs, patient travel time and time receiving vaccine, and cost of treating adverse events.

based the variable estimates used in the analyses on a thorough search and analysis of the available evidence, and we attempted to avoid bias for or against either strategy.

Role of the Funding Source

No funding was received for this study.

RESULTS

The incidence of herpes zoster over the lifetime of a 69-year-old representative patient is predicted to decrease from 17.8% without vaccination to 11.8% with vaccination (Table 2). Time spent in episodes of herpes zoster should decrease from 0.088 year without vaccination to 0.058 year with vaccination. Lifetime incidence of PHN should also decrease with vaccination, by an absolute difference of 0.56%. Cumulative time spent with PHN, thereby, is anticipated to decrease by 0.0009 year, and QALYs should increase by 0.0016 year or 0.6 day. Vaccination reduces the costs of direct medical care by \$37 and reduces the costs associated with lost work productivity by \$20.

Table 2 also shows the clinical and cost effects of vaccination versus no vaccination by age. The higher inci-

dence of zoster associated with advancing age is offset by the vaccine’s decreasing efficacy with age. The effect is fewer QALYs gained with advancing age. For example, persons 60 years of age gain 0.0024 QALY with vaccination compared with 0.0007 QALY gained for persons 80 years of age. The cost savings associated with managing zoster episodes and lost work productivity also decrease with age.

Figure 2 shows the cost per QALY gained of vaccination versus no vaccination as a function of the duration of vaccine efficacy (from 3 to 30 years) and cost of vaccine (from \$50 to \$500). Vaccination is more cost-effective with a longer duration of efficacy and a lower vaccine cost. The cost-effectiveness ratio remains less than \$100 000 per QALY gained for every scenario where vaccine cost is less than \$100, regardless of duration of vaccine efficacy. Moreover, the cost-effectiveness ratio remains greater than \$100 000 per QALY gained for every scenario where vaccine cost is \$200, unless the duration of vaccine efficacy exceeds 30 years. The \$50 000 threshold for cost-effectiveness is achieved at a cost of \$100 for the vaccine if the

duration of vaccine efficacy is at least 20 years and is achieved for all scenarios in which the vaccine cost is \$50.

One-Way Sensitivity Analyses

Many variables influence the cost-effectiveness of vaccination relative to no vaccination (Figure 3). Besides vaccine costs and duration of vaccine efficacy, cost-effectiveness is influenced by patient age and the difference in quality of life between acute zoster and no zoster. Vaccination is likely to be more cost-effective in younger persons (that is, age 60 to 64 years) than in older persons (that is, age ≥ 80 years). If quality of life associated with acute zoster is reduced to the fifth percentile (that is, 70.2 if vaccinated and 69.1 if unvaccinated), vaccination costs \$34 115 per QALY gained.

Cost-effectiveness of vaccination changed by less than 25% for the following variables: cost per zoster case, discount rate, quality-of-life adjustments for all states and for PHN alone, labor loss, burden of illness per zoster case, risk for zoster-related death, fraction of zoster cases resulting in PHN, and risk for vaccine injection site reaction.

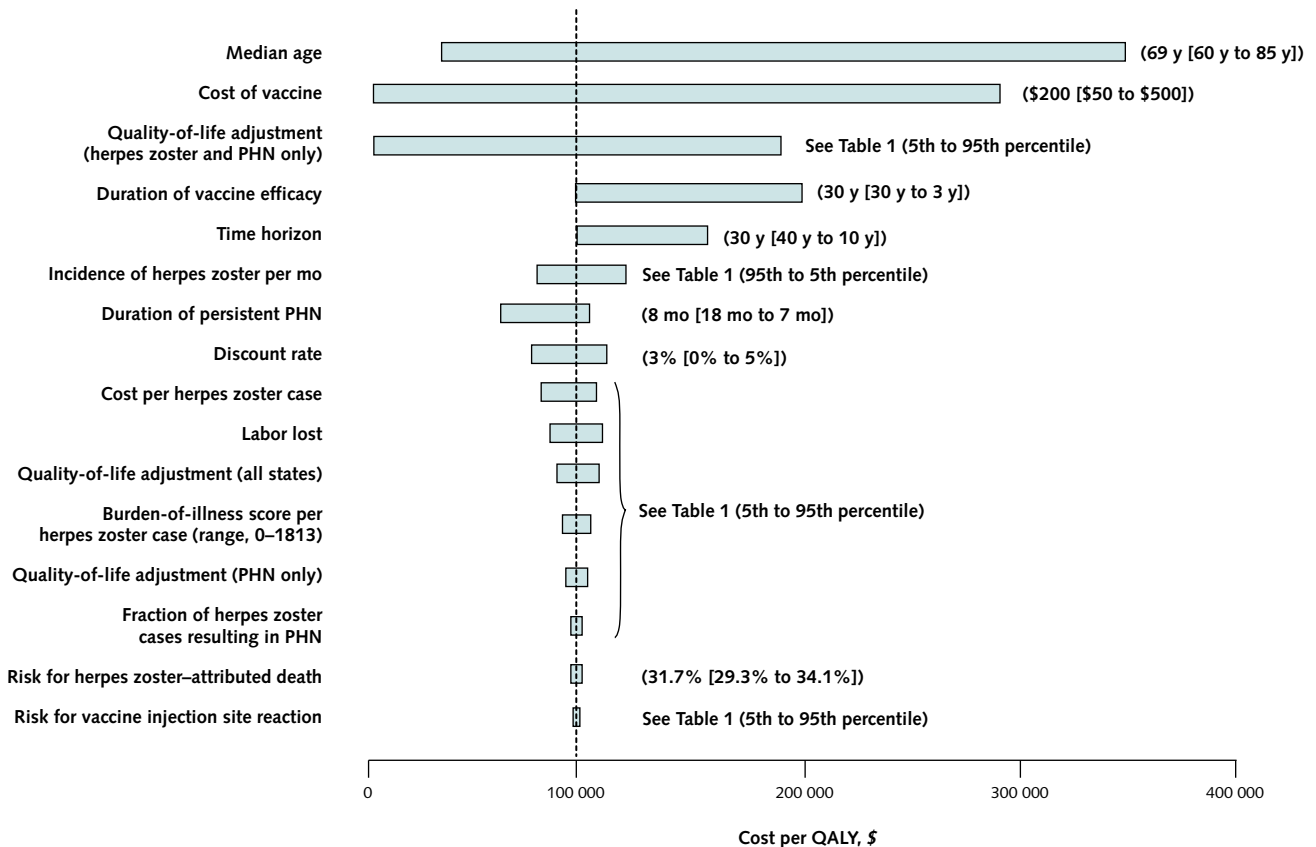
Probabilistic Analyses

At a vaccine cost of \$50, vaccination was cost-saving compared with no vaccination in more than 50% of replications and 92% of replications were less than \$100 000 per QALY gained. By contrast, at a vaccine cost of \$500, only 2% of replications had a cost-effectiveness ratio less than \$100 000. For persons 75 years of age or older, assuming a vaccine cost of \$200 and a duration of vaccine efficacy of 30 years, less than 1% of replications had a cost-effectiveness ratio less than \$100 000. The cost-effectiveness of vaccination was influenced by the duration of vaccine efficacy, with 52% of ratios less than \$100 000 if the duration of vaccine efficacy was 30 years, compared with only 16% of ratios less than \$100 000 if the duration of vaccine efficacy was 3 years.

DISCUSSION

An attack of herpes zoster can be a debilitating episode in an older adult. The lifetime risk for herpes zoster for a person 60 years of age or older exceeds 15% (4, 16). At least one quarter of patients with herpes zoster will experi-

Figure 3. One-way sensitivity analysis.



The effect of varying input variables on incremental cost-effectiveness ratios (cost per quality-adjusted life-year [QALY] ratios) for vaccination versus no vaccination. Bars indicate the variability in the cost-effectiveness ratio associated with changes in the indicated input variables. The values in parentheses show the source for the base-case value and plausible ranges. The dotted line shows the cost per QALY when vaccine cost is \$200, duration of vaccine efficacy is 30 years, and all other input variables are placed at their base-case values. PHN = postherpetic neuralgia.

ence severe pain, some for much longer than a year. The public health and clinical rationale for studying the effects of a vaccine on preventing herpes zoster in elderly persons could not be more compelling. However, the economic considerations of a vaccine to prevent herpes zoster in elderly persons are likely to be highly relevant, complementing clinical and epidemiologic factors, in deriving a population-based vaccination policy. In 2005, the U.S. Census Bureau reported that more than 49 million persons 60 years of age or older reside in the United States. The cost of a universal vaccination program could range from \$2.6 billion to \$24 billion depending on the cost per person vaccinated (32). Although our analyses show that about \$1.3 billion might be saved by the reduction of herpes zoster cases at a vaccine cost of \$50, we found few circumstances in which widespread vaccination would lead to cost savings.

Many experts recommend that full consideration of the economics of a health intervention should extend beyond budgetary implications and should also consider public health effects (33). Such an analysis for public policy typically is reported as a cost-effectiveness analysis that weighs the incremental costs of the program against its incremental effectiveness. We estimated that, in a cohort of persons 60 years of age or older, vaccination would reduce the mean incidence of acute zoster and PHN. On the basis of data from the Shingles Prevention Study, an episode of acute zoster decreases quality of life by an average of 4 points on the 0- to 100-point EuroQoL VAS, from 86.0 to 82.0. Given an 18% lifetime risk for acute zoster without vaccination from 69 years of age, the net gain is expected to be 0.6 quality-adjusted day.

We compared the net QALY gain with the expected effects of the related childhood VZV vaccine and other vaccines that are recommended for persons 60 years of age or older. Brisson and colleagues (34) estimated that, in a population of 2 928 571 infants, 3415 years of life (equal to 0.43 day of life gained per vaccinated person) would be gained if vaccination was performed to avert primary VZV infection. Smith and Roberts (35) estimated that vaccinating all adults 30 years of age or older to prevent primary VZV would increase QALYs by 0.001 day. Testing for previous immunity increased the benefit to 0.69 day per person vaccinated. Vaccination to prevent pneumococcal pneumonia increases QALYs from 0.13 day to 8.83 days (36–38).

Our findings are sensitive to many variables, including patient age, vaccine cost, incidence of herpes zoster, and expected duration of PHN. Vaccination would be more cost-effective if it were targeted to populations that are at higher risk for herpes zoster. In a recent and thorough review, Thomas and Hall (39) reported that the annual population risk for herpes zoster in persons 60 years of age or older ranges from 3.6 to 14.2 per 1000 persons. The factors that most explained the variation in risk were age, sex, ethnicity, genetic susceptibility, exogenous boosting of immunity from VZV contacts, underlying cell-mediated

immune disorders, mechanical trauma, psychological stress, and immunotoxin exposure. Except for age, the independent contribution of any one factor to risk for herpes zoster was relatively small (40). The authors concluded that information on herpes zoster risk factors is substantially lacking (39), which makes targeting a vaccination program difficult.

Another implication of our study concerns the timing of formal technology assessments that include economic outcomes. Formal analyses often are conducted after prices, reimbursements, or both are announced. As a consequence, the policy discussion may be constrained to considering the extent to which access to the technology should be restricted given the technology cost. By contrast, an independent examination of the technology's cost-effectiveness when costs are undetermined provides policymakers with a wider set of options for affordably optimizing the use of the technology to benefit the public.

Estimates of cost-effectiveness from our analyses were substantially higher than those reported by Edmunds and colleagues (16). (Details are presented in the Appendix, available at www.annals.org.) We approximated their results by applying their quality-of-life inputs associated with acute zoster (a 27-point rather than a 4-point decrease from no zoster) and by lowering the mean age of the persons vaccinated (age 65 years).

Our analysis has several limitations. First, formal evidence on how acute zoster affects utilities is relatively limited. No published utility elicitation study enrolled more than 150 respondents, which is in contrast to the more than 35 000 persons enrolled in the Shingles Prevention Study whom we used to inform the incidence and severity of zoster and the effect of vaccination. Second, the duration of vaccine efficacy beyond 3 years remains uncertain. We assumed that the duration of vaccine efficacy may be 30 years, reflecting assumptions adopted in previous models of VZV vaccination. Our sensitivity analysis shows that a shorter duration of vaccine efficacy results in vaccination being less cost-effective. Third, data are not yet available on the actual costs of a zoster vaccination program. The components of such a program are likely to include public awareness campaigns, vaccine administration, patient travel time and time receiving the vaccine, and treatment of adverse side effects of vaccination. For adult influenza vaccination, the estimated medical practice expenses varied between \$13.87 and \$46.27 in 2001 U.S. dollars (41). Such costs should be included in the overall cost per person when assessing the cost-effectiveness of zoster vaccination.

In conclusion, the Shingles Prevention Study (6) established that VZV vaccination of older adults should reduce the incidence of acute zoster and PHN. We extend the implications of that trial to show that vaccination should improve quality-adjusted survival. Varicella-zoster virus vaccination of older adults is unlikely to cost less than \$100 000 per QALY gained compared with no vaccination, unless the total vaccination cost is less than \$200 and

duration of vaccine efficacy exceeds 20 years. Our study identifies the factors that would most influence the cost-effectiveness of vaccination, which may prove useful in shaping future research agendas. For example, scientific contributions that would inform an economical public policy are 1) developing an epidemiologic model that reliably targets persons who are at high risk for herpes zoster and its most severe complications, 2) determining the long-term efficacy of vaccination, and 3) conducting studies with larger sample sizes on the average effects on quality of life of acute zoster and PHN. Until such data are available, public policy decisionmakers are likely to face the important question about whether the benefits of VZV vaccination for preventing herpes zoster in older adults are worth the cost.

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Potential Financial Conflicts of Interest: None disclosed.

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APPENDIX

The Appendix describes 1) the evidence searches and summaries, 2) the correlation of zoster-specific burden of illness and utilities, 3) the between-model validation, and 4) additional details on the probabilistic sensitivity analyses.

Evidence Searches and Summaries

We searched the literature published from 1966 to March 2006 by using PubMed to research the following questions: What is the duration of PHN? What is the duration of vaccine efficacy? What is the lost work productivity due to an episode of acute zoster? What are the costs of an acute zoster episode and PHN?

Duration of PHN

We found 56 studies on duration of PHN (Appendix Table 1). Studies vary in the reporting of pain persistence after onset of zoster, using such end points as cessation of all pain, PHN, and zoster-associated pain (42). The duration of pain after onset of acute zoster varies by age and by whether the patient receives antiviral therapy (42).

In the era before antiviral therapy for zoster, De Moragas and Kierland (43) reported that more than 50% of patients have pain up to 11 months after onset of acute zoster. Hope-Simpson (10) reported in 1965 that more than 20% of patients have pain 12 months after the onset of acute zoster. Summarizing studies published before 1995 (10, 13, 44, 45), Huse and colleagues (46) estimated that the probability of persistent PHN was 55% at 2 months, 30% at 5 months, and 22% to 25% at 12 months. At 5 months after onset of zoster in patients receiving antiviral therapy, the probability of persistent PHN was 15% if patients were younger than 50 years of age and 27% if patients were older than 50 years of age (46).

In a cost-effectiveness analysis of vaccination to prevent herpes zoster, Edmunds and colleagues (16) assumed that the duration of PHN is 1.40 years (range, 0.93 to 2.40 years), citing 3 studies (10, 42, 47). Dworkin and Portenoy (42) and Wood and colleagues (47) estimated that the median duration of zoster-associated pain or complete pain cessation is less than 3 months.

Duration of Vaccine Efficacy

We first examined the evidence of duration of efficacy of the live attenuated VZV vaccine for children. We then examined the

Appendix Table 2. Search on Duration of Vaccine Efficacy*

Search	Search Terms	Citations, n
1	Zoster OR herpes zoster, with or without MeSH terms	8124
2	Vaccine	65 092
3	Persistence	17 516
4	#1 AND #2	861
5	#3 AND #4	26

* Search limited to human participants and English language. MeSH = Medical Subject Heading.

assumptions used in cost-effectiveness analyses of vaccination in children and adults. We found 26 studies pertaining to the duration or persistence of vaccine efficacy (Appendix Table 2).

Ampofo and colleagues (48) studied 461 healthy adults enrolled in VZV vaccine trials between 1979 and 1999. Participants' mean age was 32 years (range, 20 to 46 years), and they were followed for up to 11.8 years. Forty vaccinated persons (9%) developed breakthrough chickenpox at a mean of 3.3 years after vaccination. Saiman and colleagues (49) studied 120 health care workers for 1 year to 20.6 years (mean, 4.6 years) after VZV vaccination. Twelve (10%) participants developed breakthrough VZV, with 1 reported zoster case.

On the basis of Japanese and U.S. studies, the CDC reports that protection for children lasts at least 15 years and predicts that approximately 1% of persons vaccinated per year will develop breakthrough primary VZV infection even if participants initially respond to the vaccine (28).

Appendix Table 3 summarizes the assumptions used in publications of cost-effectiveness and cost-benefit analyses of VZV vaccine for children (12 studies) and adults (1 study).

Two studies included no information on duration of vaccine efficacy. Brisson and colleagues (34) reported a 3.1% annual rate of developing "partial" susceptibility to VZV. Estimates from their study were cited in 3 other studies. In several instances, the source for estimates of efficacy duration was not cited. Lieu and colleagues (57) assessed the cost-effectiveness of routine VZV vaccination for U.S. children, assuming that 15% would experience partial waning of immunity by the time of death, but they cited no evidence to substantiate their assumption. In 2005, Goldman (56) assumed that vaccinated persons have 100% protection from breakthrough infection and that recurrence of zoster is negligible.

Edmunds and colleagues (16) assessed the cost-effectiveness of VZV vaccination in older adults, initially assuming lifetime protection. They illustrated the cost-effectiveness of vaccination if the duration of vaccine efficacy was as low as 2.5 years.

Lost Work Productivity from an Acute Zoster Episode

We found 101 studies pertaining to the effect of acute zoster on lost work productivity (Appendix Table 4).

None of these papers reported the effect of an episode of acute zoster on the amount of work lost or productivity. Several studies were about the impact of primary VZV infection, particularly its effect on days of work lost.

Appendix Table 1. Search on Duration of Postherpetic Neuralgia*

Search	Search Terms	Citations, n
1	Zoster	489
2	Herpes zoster	476
3	#1 OR #2	502
4	Time [MeSH]	43 806
5	#3 AND #4	56

* All searches were limited to human participants and English language. Searches 1–3 were also limited to clinical trials or randomized, controlled trials. MeSH = Medical Subject Heading.

Appendix Table 3. Summary of Evidence Used on Waning Immunity in Cost-Effectiveness Studies of Live Attenuated Varicella-Zoster Virus Vaccine*

Author, Year (Reference)	Vaccine	End Point	Mean Assumption (Range)	Source (Reference)
Brisson et al., 2001 (50)	Childhood	NR	NR	NR
Brisson et al., 2000 (34)	Childhood	Annual incidence of breakthrough VZV	3.1% (2.1% to 7.2%)	Manufacturer's published data
Brisson and Edmunds, 2002 (51)	Childhood	Rate at which temporarily protected individuals become partially susceptible to VZV (1 y)	3.1% (2.1% to 8.5%)	Brisson et al., 2000 (34)
Coudeville et al., 2004 (52)	Childhood	Proportion of protected, vaccinated participants becoming partially susceptible to VZV	15.0% (6.0% to 35.0%)	Hallaran et al., 1994 (53)
Coudeville et al., 1999 (54)	Childhood	Rate at which protected, vaccinated persons become partially susceptible to chickenpox	3.1% (2.1% to 5.0%)	NR
Edmunds et al., 2001 (16)	Adult	Mean duration of vaccine protection	Lifelong (2.5 y to lifelong)	NR
Ginsberg and Somekh, 2004 (55)	Childhood	Rate at which protected, vaccinated persons become partially susceptible to chickenpox	3.1% (NR)	Brisson et al., 2000 (34)
Goldman, 2005 (56)	Childhood	Protection against breakthrough or recurrence of herpes	100.0% (NR)	NR
Lieu et al., 1994 (57)	Childhood	Partial waning of immunity by time of death	15.0% (NR)	Expert panel
Smith and Roberts, 2000 (35)	Childhood	Protection from chickenpox 10 y after vaccination	90.0% (NR)	CDC, 1996 (58)
Thiry et al., 2004 (59)	Childhood	Rate at which protected, vaccinated persons become partially susceptible to VZV (waning of immunity)	3.1% (NR)	Brisson et al., 2000 (34)
Wutzler et al., 2002 (60)	Childhood	Annual rate that the effect wanes	0.5% (NR)	NR
Zhou et al., 2005 (61)	Childhood	NR	NR	NR

* CDC = Centers for Disease Control and Prevention; NR = not reported; VZV = varicella-zoster virus.

We obtained information from publicly available reports on the proportion of older adults who are employed and the average annual income for working older adults (Appendix Table 5) (27). The U.S. Department of Labor Bureau of Labor Statistics reported in 2002 that among 59 reported cases of zoster resulting in absence from work, the median days absent from work was 15 days (27). We also calculated the lost wages from a zoster episode by age and sex (Appendix Table 6).

Costs of an Acute Zoster Episode and Postherpetic Neuralgia

Smith and Roberts (26) provided a synthesis of 5 studies on the costs (in 1995 U.S. dollars) of managing herpes zoster in immunocompetent persons. We searched MEDLINE from 1966 to March 2006 by using the same search terms from their review:

Appendix Table 4. Search on Work Lost and Herpes Zoster†

Search	Search Terms	Citations, n
1	Zoster OR herpes zoster (with and without MeSH terms)	8124
2	Job* OR labor OR work OR employment	239 235
3	Work [MeSH] OR workplace [MeSH] OR employment [MeSH] OR salaries and fringe benefits [MeSH]	36 873
4	#2 OR #3	245 773
5	#1 AND #4	101

† Search limited to human participants and English language. MeSH = Medical Subject Heading.

Appendix Table 5. Probability of Working and Weekly Wage by Sex and Age Group*

Variable	Men	Women
Probability of working, %		
Age 60–64 y	58	46
Age 65–69 y	34	24
Age 70–74 y	21	13
Age ≥ 75 y	9	5
Average weekly wage, \$		
Age 60–65 y	847	616
Age ≥ 65 y	580	434

* Data are from the Bureau of Labor Statistics (27). See Appendix Table 6 for calculation of the lost wages from a zoster episode by sex and age.

Appendix Table 6. Computed Lost Wages from Zoster Episode by Sex and Age Group

Age Group	Lost Wages, \$ U.S.		
	Men	Women	Average
60–64 y	2457	1412	1934
65–69 y	974	514	744
70–74 y	600	278	439
≥75 y	272	98	185

Appendix Table 7. Search on Cost and Herpes Zoster†

Search	Search Terms	Citations, n
1	Zoster OR herpes zoster (with and without MeSH terms)	8124
2	Cost*	133 974
3	#1 AND #3	143

† Search limited to human participants and English language. MeSH = Medical Subject Heading.

zoster AND *herpes zoster*, *antiviral agents* (exploded), and *cost** (Appendix Table 7).

Fifty-five of the 143 papers we found were published after Smith and Roberts' report (26). Six papers contained primary cost information, but the costs were estimated for other countries (Canada, Australia, and Israel) or the papers provided information only on the management of primary VZV infection. A search of Smith and Roberts' paper (26) in Science Citation Index revealed no additional citations.

We used cost categories similar to those of Smith and Roberts (26) and updated inputs by using contemporary data sources (Appendix Table 8).

Appendix Table 9 shows the average wholesale prices for

antivirals and prednisone from *Mosby's Drug Consult 2006* (18–20) and retail drug prices from *www.drugstore.com* (21) and *www.costco.com* (22).

We found no publicly available information on the distribution and use of antivirals or steroids. Clinical reviews (for example, UpToDate 14.1) have recommended antivirals for patients seeking care for herpes zoster within 72 hours of clinical presentation. However, prednisone is recommended for patients who present with severe symptoms and for whom steroids are not contraindicated. For the base-case analysis, we assumed that all patients would receive antiviral treatment at the average cost of a course of antivirals and that 20% of patients would receive prednisone. We used the generic drug price estimate from *www.costco.com* (\$180). We also explored the cost-effectiveness results in sensitivity analyses if health plans tend to primarily use the least expensive generic drug regimen (\$135) or the most expensive brand-name drug regimen (\$288).

Correlation of Burden-of-Illness End Point and Utilities

The zoster-specific burden of illness is correlated with the EuroQoL VAS and the Short Form-12 mental health and physical health summary scales (9, 67). Appendix Figure 1 shows the empirical relationship between change in burden-of-illness score and the EuroQoL VAS score (9). The VAS score ranged from

Appendix Table 8. Resources and Costs of Herpes Zoster Episode*

Variable	1995 Value	Source†	2006 Value	Source†
Acute herpes zoster medical costs	\$88‡	Grant et al., 1997 (62)	\$115§	2 outpatient office visits, CPT 99213 established outpatient (17)
Antiviral treatment costs	\$134‡	Huse et al., 1997 (46)	\$180§	AWP (18–20); retail prices (21, 22)
Probability of hospitalization	0.26%	Grant et al., 1997 (62)	1.15%	Shingles Prevention Study (Oxman et al., 2005 [6])
Cost per hospitalization	\$2478‡	Grüger and Backhouse, 1997 (63)	\$6884§	CMS (29)
Lost work productivity	NR	NR	\$744§	See Appendix Table 6
Postherpetic neuralgia costs per mo	\$106‡	Smith and Roberts, 1998 (64); Davies et al., 1994 (65)	\$166§	Smith and Roberts, 2000 (26)

* AWP = average wholesale price; CMS = Centers for Medicare & Medicaid Services; CPT = Current Procedural Terminology; NR = not reported.

† Numbers in parentheses are references.

‡ 1995 U.S. dollars.

§ 2006 U.S. dollars.

|| Cost inflated by using U.S. city averages of the Producer Price Index for medical care services (66). For 1995 to 2006, prices increased by 56.8%.

Appendix Table 9. Current Average Wholesale Price and Retail Prices for a Course of Antivirals and Prednisone Indicated for Herpes Zoster*

Drug†	Dosage	Total Tablets, n	Price from <i>Mosby's Drug Consult 2006</i> (18–20), \$		Price from <i>Drugstore.com</i> (21), \$		Price from <i>Costco.com</i> (22), \$	
			Brand	Generic	Brand	Generic	Brand	Generic
Acyclovir	800 mg, 5 times daily, 10 d	50	237	73	366	42	348	19
Valacyclovir	1000 mg, 3 times daily, 7 d	21	163	NA	189	NA	274	NA
Famciclovir	500 mg, 3 times daily, 7 d	21	171	NA	171	NA	254	NA
Steroids	Taper‡, once daily, 21 d	21	NA	5	NA	8	NA	5
Average price§			189	135	240	137	288	180

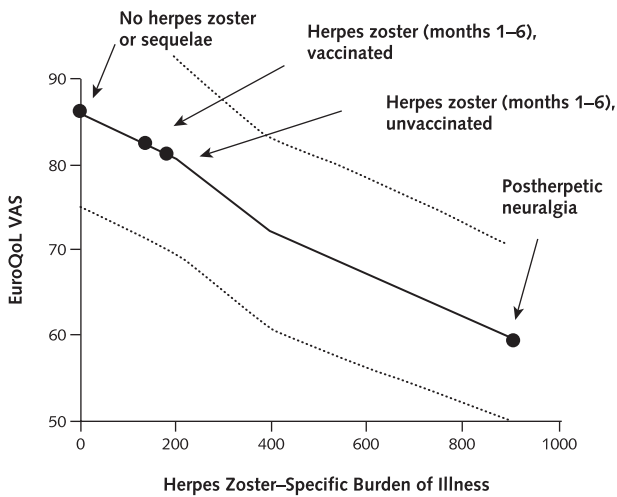
* NA = not available.

† Acyclovir is sold as a brand-name and generic drug. Prednisone is sold as a generic drug. Valacyclovir and famciclovir are sold as brand-name drugs.

‡ Assumed to be prednisone administered as a taper over 21 days starting with 30–40 mg.

§ The average prices in the brand-name drug columns are based on the average of prices for all antiviral brand-name drugs plus the price of prednisone. The average prices in the generic drug columns are based on the average of prices for famciclovir and valacyclovir and the price of generic acyclovir plus the price of prednisone.

Appendix Figure 1. Correlation of herpes zoster–specific burden-of-illness score with utilities.



Data presented are means (SDs). The range for burden-of-illness score is 0 to 1813. Data are from Coplan et al. (9). VAS = visual analogue scale.

84.0, which is associated with a burden-of-illness score of 0 (similar to no herpes zoster), to 59.4. We computed utilities as the VAS score divided by 100.

Between-Model Validation

Recent modeling guidelines recommend that findings be validated against other independently developed models. This validation is called *between-model corroboration* or *convergent validity* (68). A 2001 study, herein called the United Kingdom study, presented findings from a model of the epidemiology and cost-effectiveness of vaccination of persons 60 years of age or older who live in England and Wales (16). Inputs from the United Kingdom study were based on hypothetical projections of vaccination efficacy. In this and several other input values, the United Kingdom study estimates differed from those of our study. We applied their assumptions to our model to assess their ability to replicate findings conducted by 2 independent analyst groups (Appendix Table 10).

Comparison of Model Perspective, Design, and Analytic Framework

Edmunds and colleagues (16) studied the epidemiology of zoster and PHN in England and Wales and assessed whether mass adult vaccination against zoster is likely to be cost-effective. The perspective of the analysis was that of the health care provider. Under this perspective, patient costs are assumed to be minimal because more than 70% of zoster cases would occur in elderly persons, and therefore, productivity losses would be small. The methods section (see Edmunds and colleagues' Table 4 [16]) presented evidence by age group (from 45 to 49 years to ≥ 85 years) on the incidence of zoster and PHN, medical resource use (hospitalization and consultations), and case-fatality risk. The results section presented data on persons 65 years of age or older

Appendix Table 10. Comparison of Inputs from the 2001 United Kingdom Model and the 2006 United States Model*

Input	2001 United Kingdom Model	2006 United States Model†
Median age, y	65	69
Incidence of zoster per 1000 person-years by age group		
Not vaccinated		
Age 60–64 y	5.92	9.95
Age 65–69 y	6.70	11.63
Age 70–74 y	7.53	11.44
Age 75–79 y	8.42	11.31
Age 80–84 y	9.37	12.23
Age 85–89 y	11.58	12.23
Age ≥ 90 y	11.58	14.29
Vaccinated		
Age 60–64 y	1.78	3.44
Age 65–69 y	2.01	4.35
Age 70–74 y	2.26	6.44
Age 75–79 y	2.53	7.18
Age 80–84 y	2.81	9.77
Age 85–89 y	3.47	10.04
Age ≥ 90 y	3.47	11.73
Zoster cases resulting in PHN, %		
Vaccinated	28.3	2.9
Not vaccinated	28.3	5.1
Duration of vaccine efficacy, y	Lifetime	3–30
Duration of PHN, mo	14	8
Quality of life (range, 0–100)		
If no zoster	100	86
Zoster	71.3	81.7
Postherpetic neuralgia	67.3	59.4
Injection site reaction, %	NR	–10%
Costs‡		
Vaccine	£0–£120	\$50–\$500
Zoster case		
Vaccinated	£125	\$642
Not vaccinated	£125	\$742
Case-specific mortality per 10 000 zoster cases by age group		
Age 60–64 y	0	0
Age 65–69 y	0.25	0.25
Age 70–74 y	0.75	0.75
Age 75–79 y	2.50	2.50
Age 80–84 y	9.50	9.50
Age ≥ 85 y	28.00	28.00

* PHN = postherpetic neuralgia; NR = not reported.

† Based on the Shingles Prevention Study (Oxman et al., 2005 [6]).

‡ Costs for the United Kingdom model were reported in 1998 British pound sterling, whereas costs for the United States model are reported in 2006 U.S. dollars.

(see Edmunds and colleagues' Figure 4 [16]) and data by age from 45 years to 80 years (see Edmunds and colleagues' Figure 5 [16]), but the analysis assumed that vaccination would occur at 65 years of age. The intervention was mass adult vaccination to prevent zoster. The comparator was "current practice" involving

treatment of acute zoster and PHN. The primary outcome measure was the QALY gained, and the primary economic measure was the cost per QALY gained with vaccination. Edmunds and colleagues' Table 2 (16) provides variable values for the following 7 health states: 1) no zoster, 2) zoster with no pain, 3) zoster with mild pain, 4) zoster with severe pain, 5) PHN with mild pain, 6) PHN with severe pain, and 7) death.

Comparison of Model Inputs and Variable Values

Appendix Table 10 shows a comparison of the input values in our study and those in the United Kingdom study. The incidence of herpes zoster in the vaccine group of the Shingles Prevention Study was 40% to 80% higher than that reported in the United Kingdom study. Vaccine efficacy was substantially lower in the Shingles Prevention Study for patients 70 years of age or older than the estimates used in the base-case analyses of the United Kingdom study. The incidence of PHN in the Shingles Prevention Study was approximately one third lower than that in the United Kingdom study. The upper anchor of quality of life (no herpes zoster) for the United Kingdom study was 100 compared with 86 in the Shingles Prevention Study. The difference in quality of life between zoster and no zoster was 28.7 in the United Kingdom study but was only 4.3 in our study. Costs for the vaccine and management of herpes zoster reported in the United Kingdom study, adjusted for inflation and converted to U.S. dollars, were less than one half of those reported in our study.

Comparison of Results

We applied the variable inputs from the United Kingdom study (shown in Appendix Table 10) to our analytic framework. At a price of £120 for vaccination and a vaccine efficacy of 70%, the cost per QALY gained equaled £8003 (in 1998 British pound sterling). This estimate is modestly higher than that reported for the United Kingdom study (approximately £6000) (see Edmunds and colleagues' Figure 4 [16]).

Appendix Table 11. Effect on Cost per Quality-Adjusted Life-Year Gained with Vaccination Compared with No Vaccination by Changing One Variable at a Time Back to the U.S. Estimate*

Input	Cost per QALY Gained, £†
Median age	8231
Incidence of zoster per 1000 person-years, by age group	8977
Fraction of zoster cases resulting in PHN	10 306
Duration of PHN	10 160
Quality of life	22 368
Cost per zoster case	6947

* Costs for the United Kingdom model were reported in 1998 British pound sterling, whereas costs for the U.S. model are reported in 2006 U.S. dollars. Exchange rate is \$1 = £0.558 (as of 25 May 2006). Inflation from 1998 to 2006 was 38.4%. PHN = postherpetic neuralgia; QALY = quality-adjusted life-year. † Base case, £8003.

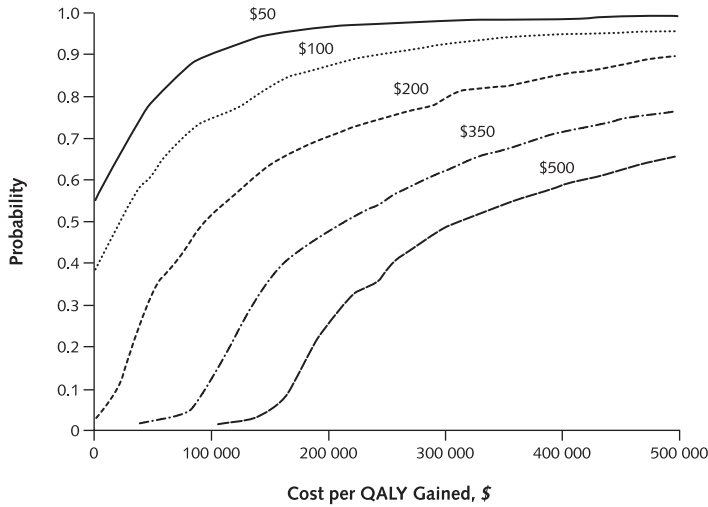
We also explored the contribution of each variable to the differences between the United Kingdom and U.S. models. Appendix Table 11 shows the effect of changing the value of one variable at a time back to the U.S. estimate. For cost, we assumed a currency exchange rate of \$1 to £0.558 (as of 25 May 2006) and inflation in medical services of 38.4% from 1998 to 2006 (27).

The most influential variable was the set of quality-of-life inputs. Using the U.S. model estimates increased the United Kingdom cost per QALY gained by almost 3-fold. No other U.S. input independently increased the cost per QALY gained by more than 50%.

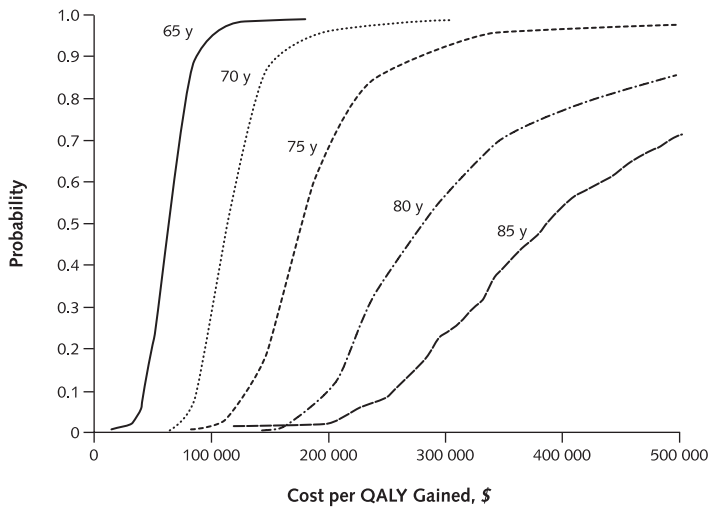
Additional Details on Probabilistic Sensitivity Analyses

Appendix Figure 2 shows the results of the probabilistic sensitivity analyses by vaccine cost (range, \$50 to \$500), age (range, 65 to 85 years), and duration of vaccine efficacy (range, 3 to 30 years).

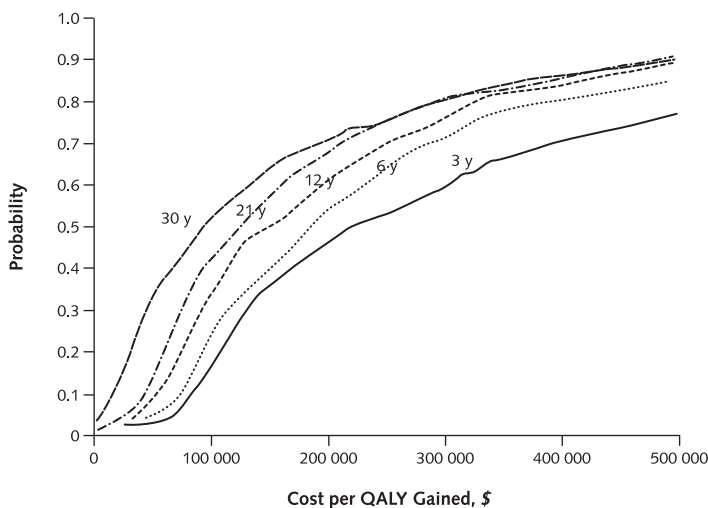
Appendix Figure 2. Probabilistic sensitivity analyses by vaccine cost (top), age (middle), and duration of vaccine efficacy (bottom).



Vaccine Price	Percentile		Probability ICER < \$50 000	Probability ICER < \$100 000
	25th	75th		
\$50	Cost-saving	\$19 947	78%	90%
\$100	Cost-saving	\$66 441	60%	74%
\$200	\$37 766	\$245 556	32%	51%
\$350	\$123 949	\$339 329	2%	11%
\$500	\$199 903	\$508 804	<1%	<1%



Age	Percentile		Probability ICER < \$50 000	Probability ICER < \$100 000
	25th	75th		
65 y	\$53 145	\$68 772	21%	95%
70 y	\$99 423	\$124 557	<1%	25%
75 y	\$153 855	\$194 609	<1%	<1%
80 y	\$228 158	\$325 126	<1%	<1%
85 y	\$306 378	\$454 358	<1%	<1%



Vaccine Duration	Percentile		Probability ICER < \$50 000	Probability ICER < \$100 000
	25th	75th		
30 y	\$37 766	\$159 506	32%	51%
21 y	\$67 174	\$183 758	12%	42%
12 y	\$84 811	\$222 056	7%	33%
6 y	\$103 803	\$255 548	3%	23%
3 y	\$118 839	\$335 000	3%	16%

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.