Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix. Supplemental Appendix

METHODS

Long-term efficacy of the live attenuated herpes zoster vaccine (ZVL)

The Shingles Prevention Study was a randomized, placebo-controlled, double-blind trial involving 38,546 people aged ≥ 60 years.[1] The trial first reported efficacy data up to 4 years post-vaccination. A portion of participants were then followed in the Short-term Persistence Sub-study [2] and Long-term Persistence Sub-study (LTPS) [3] up to 11 years post-vaccination. Three components of efficacy were reported: efficacy against HZ incidence, post-herpetic neuralgia (PHN) incidence, and burden of illness (BOI). Because HZ is necessary to experience either PHN or BOI, the measures are by definition interrelated, in particular because efficacy against PHN and BOI were greater than the efficacy against HZ, implying that even when the vaccine failed to prevent HZ, it still had some residual efficacy against these complications. BOI was a severity -by-duration measure which captured all pain and discomfort of HZ and was calculated as the area under the curve of HZ-related pain over time for up to 182 days after rash onset. Therefore, any reduction in BOI incorporated the vaccine's impact on HZ incidence and on the severity of pain among vaccinated HZ cases in the first 6 months after disease onset. Efficacy against PHN incidence included the vaccine's impact on HZ incidence leading to fewer HZ cases and subsequently fewer PHN cases and on PHN incidence among vaccinated persons who developed HZ. Therefore, we modeled long-term efficacy of the ZVL using three different efficacy functions. We first estimated the long-term efficacy against HZ incidence by year, using yearly efficacy data in the first 6 years and an aggregated efficacy for 7-11 years post-vaccination ($y = 0.6478 - 0.0544\ x\ year$). This efficacy was further adjusted for vaccination age difference.[4,5] Efficacy against BOI was obtained by fitting a linear regression on the three aggregated data points reported for SPS, STPS and LTPS ($y = -0.0437\ x\ year + 0.7083$).[1-3] Regarding PHN incidence, the LTPS also reported yearly efficacy but these estimates were not statistically significant.[3] Therefore, we assumed a stable efficacy for the first 5 years using the aggregated data and a declining function at year 6 ($y = -0.1\ x\ year + 1.218$). The three efficacy components were then related to each other in a function to estimate the additional efficacies against BOI or PHN incidence among HZ cases.

$$x = \frac{Eff - Eff_{HZ}}{1 - Eff_{HZ}}$$

where *x* is efficacy against BOI (or PHN incidence) among HZ cases, *Eff* is the efficacy against BOI (or PHN incidence) and Eff_{HZ} is the efficacy against HZ incidence as described above. For vaccinated patients, we applied the efficacy against HZ incidence first, i.e. the vaccine would make them less likely to develop HZ. However, because the efficacy against HZ was not 100%, vaccinated patients might still develop HZ, in which case the efficacy against BOI was applied to reduce the loss of quality-adjusted life years due to HZ. Finally, the vaccine would further reduce PHN incidence among these vaccinated HZ cases. The validation of these efficacy functions and graphs were presented in our previous study.[6]

Long-term efficacy of the adjuvanted subunit vaccine (HZ/su)

Efficacy of 2 doses

We estimated the initial efficacy of HZ/su based on ZOE-50 and ZOE-70.[7,8] These randomized controlled trials did not measure BOI, and the efficacy against PHN was actually lower than the efficacy against HZ incidence, meaning that HZ/su had no additional efficacy

against PHN incidence among HZ cases who were vaccinated. In fact, patients who experienced HZ despite vaccination with HZ/su were more likely than average patients to experience PHN. However, the number of cases of PHN was so small that the confidence interval around this estimate was extremely wide, and it seems unlikely that the vaccine would increase the risk of PHN among breakthrough cases. Therefore, we use a single efficacy function to represent HZ/su efficacy against HZ incidence.

We chose to use the efficacy reported for the total cohort instead of the modified vaccinated cohort because the latter excluded patients not receiving the second dose and those experiencing HZ within 1 month after the second dose. We assumed the average efficacy for the first three years after vaccination was 94.1% (95% confidence interval (CI): 85.6-98.1) for patients aged 60-69 years and 89.9% (95% CI: 85.4-93.2) for patients aged ≥70 years because the mean follow-up time of ZOE-50 and ZOE-70 was 3.2 and 3.7 years, respectively. Yearly efficacy data was available for patients aged ≥70 years, and efficacy declined right after year 1. As we described in the text, the linear regression function fit on these values returned a slope or waning rate of -3.64% with 95% CI of (-10.68% – 3.4%) which was not statistically significant. In addition, this 95% CI encompasses the 95% CI of the slope of the efficacy function for ZVL against HZ incidence. Therefore, we assumed that HZ/su had the same waning rate as the ZVL and used it to calculate the intercept of the efficacy function for HZ/su. The final efficacy functions for HZ/su were $y = 1.049 - 0.0544\ x\ year$ (age 60-69 years) and $y = 1.008 - 0.0544\ x\ year$ (age ≥70 years). eTable 1 presents the efficacy against HZ incidence of ZVL and HZ/su in the first 10 years post vaccination in the base-case.

Efficacy of 1 dose

HZ/su series includes 2 doses administered 2 months apart. In clinical practice, it is possible that patients might not get 2 doses, so efficacy estimate of a single HZ/su dose is necessary to calculate its effectiveness accurately. However, there have been no clinical studies conducted to assess the efficacy of a single dose. In an exploratory analysis using data from ZOE-50 and ZOE-70, the initial efficacy of 1 dose was 90% (95% CI: 62.1%-99%) in patients aged 60-69 years and 69.5% (24.9%-89.1%) in patients aged ≥70 years. This analysis included data for the whole study period from 5% of patients who did not complete 2 doses and for the observation window between dose 1 and 2 from 95% of patients who received both doses. The mean follow-up time was, therefore, <3 months. Due to lack of data, we conservatively assumed that the efficacy waning rate for 1 dose was twice as much as for 2 doses, yielding efficacy functions for a single HZ/su dose of $y = 0.9272 - 0.1088\ x\ year$ (age 60-69 years) and $y = 0.7222 - 0.1088\ x\ year$ (age ≥70 years)

RESULTs

One-way sensitivity analysis

eTable 2 presents additional data on costs, QALY and ICERs of three strategies at different HZ/su prices among people vaccinated at 60 years. The higher the cost of HZ/su, the less cost-effective the HZ/su was. If the HZ/su price was double the base-case, the ICER of HZ/su compared to ZVL was more than $100,000/QALY.

In addition, compared to no vaccination, the ICER of HZ/su was $42,676/QALY when the waning rate of a single HZ/su dose was double the base-case, $36,834/QALY when adherence rate was half of base-case, $49,198/QALY when the initial efficacy of a single HZ/su dose was half the base-case, and $63,968/QALY when productivity loss was excluded. When the

initial efficacy of both one and two doses of HZ/su was reduced by half, HZ/su was dominated by the ZVL, and the ICER of ZVL compared to no vaccination was $67,150/QALY. Additional scenario analyses on the waning rate of both one and two doses of HZ/su showed that HZ/su was dominant to both no vaccine and ZVL if the waning rate of 2 doses was <2.88%/year or efficacy duration was ≥35 years. The ICER of HZ/su compared to no vaccine would be lower than $50,000/QALY at a waning rate of ≤6.64%/year. If the waning rate of 2 HZ/su doses was >8.7%/year or duration of protection was less than 12 years, HZ/su would be dominated.

Two-way sensitivity analysis

eFigures 3-6 show that ZVL had no chance of being chosen at $50,000/QALY because it was either dominated or removed due to extended dominance by HZ/su, confirming the base-case result. If no one got the second dose, HZ/su would still be cost-effective compared to no vaccine up to a price of $268/series (eFigure 3). The higher the adherence rate, the higher the price of HZ/su could be to remain cost-effective. If everyone got 2 doses, HZ/su could command a price up to $395/series at $50,000/QALY threshold.

In addition, the cost-effectiveness of HZ/su depends more on its price than its efficacy, and the higher the efficacy, the higher HZ/su price could be. HZ/su would always be cost-effective at a price <$288/series regardless of the efficacy of 1 dose (eFigure 4). If the efficacy of 2 doses was >70%, HZ/su would be cost-effective if its price was <$202/series (eFigure5). Finally, the cost-effectiveness of HZ/su was sensitive to efficacy of 2 doses than the adherence rate. If efficacy of 2 doses was <82.3%, HZ/su would not be cost-effective even if all patients get 2 doses. At an efficacy of 85.6% (the lower end of 95% CI), HZ/su would be cost-effective if adherence rate was >16.6% (eFigure6).

Probabilistic sensitivity analysis

Taking 10,000 samples of the Monte Carlo simulation at vaccination age 60 years, 73.8% of the ICERs of HZ/su compared to no vaccine fell below the $50,000/QALY decision threshold (eFigure 7-a), while only 27.1% of the ICERs of ZVL compared to no vaccine were below the threshold (eFigure 7-b). In addition, eFigure 8 shows the probability of each strategy being cost-effective at $50,000/ QALY as a function of HZ/su price. The higher the cost of HZ/su, the lower the probability of HZ/su being cost-effective. At a price of >$350/course, the probability of HZ/su being cost-effective at $50,000/QALY was smaller than that of no vaccination.

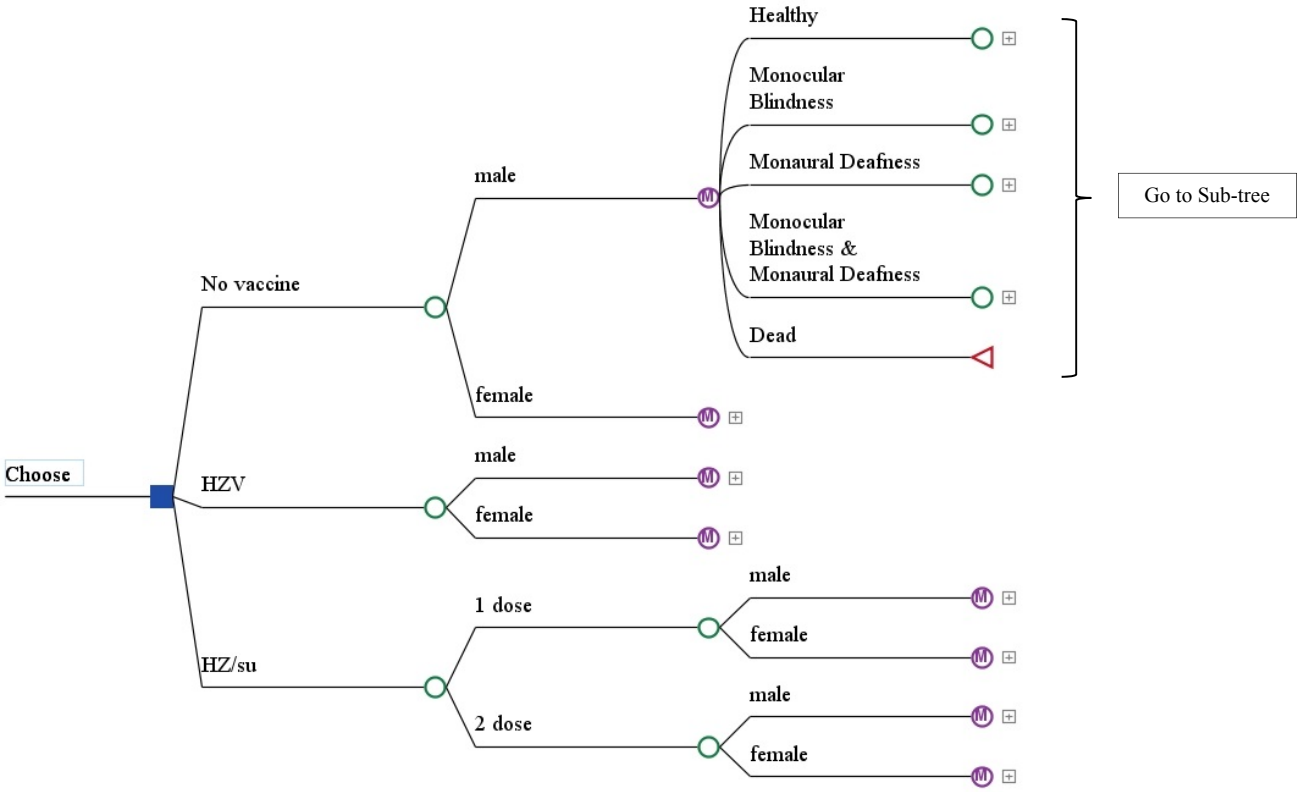
eTable 1. Vaccine Efficacy Against HZ Incidence by Years Post Vaccination by Age at Vaccination

Year after vaccination	Efficacy of ZVL (%)			Efficacy of HZ/su (%)	
	Age 60 y	Age 70 y	Age 80 y	Age 60 y	Age ≥70 y
1	74.4	54.6	27.4	99.5	95.4
2	70.0	49.0	23.2	94.0	89.9
3	65.2	43.6	19.5	88.6	84.5
4	60.1	38.3	16.3	83.1	79.0
5	54.5	33.1	13.4	77.7	73.6
6	48.6	28.0	10.9	72.3	68.2
7	42.1	23.1	8.6	66.8	62.7
8	35.0	18.2	6.5	61.4	57.3
9	27.3	13.4	4.6	55.9	51.8
10	18.8	8.7	2.9	50.5	46.4

eTable 2. Costs and Effectiveness of the Three Strategies at Different Prices of the HZ/su for People Vaccinated at Age 60 Years

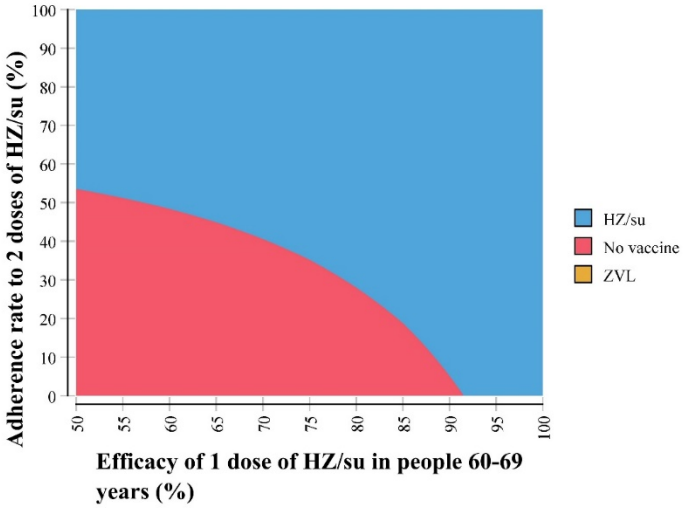
Strategy	Cost ($)	Incremental cost ($)	QALYs	Incremental QALYs	ICER ($/QALY)
Price = $140/2-dose course					
HZ/su	533		12.8661		
No vaccine	549		12.8630		Dominated
ZVL	696		12.8652		Dominated
Price = $280/2-dose course					
No vaccine	549		12.8630		
HZ/su	642	93	12.8661	0.0031	30,084
ZVL	696		12.8652		Dominated
Price = $420/2-dose course					
No vaccine	549		12.8630		
ZVL	696		12.8652		Extended dominance*
HZ/su	750	202	12.8661	0.0031	65,303
Price = $560/2-dose course					
No vaccine	549		12.8630		
ZVL	696	148	12.8652	0.0022	67,151
HZ/su	859	163	12.8661	0.0001	183,330

Note: * An "extended dominance" strategy means it had an ICER higher than the next more effective strategy. ZVL, live attenuated herpes zoster vaccine; HZ/su, adjuvanted herpes zoster subunit vaccine; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio.

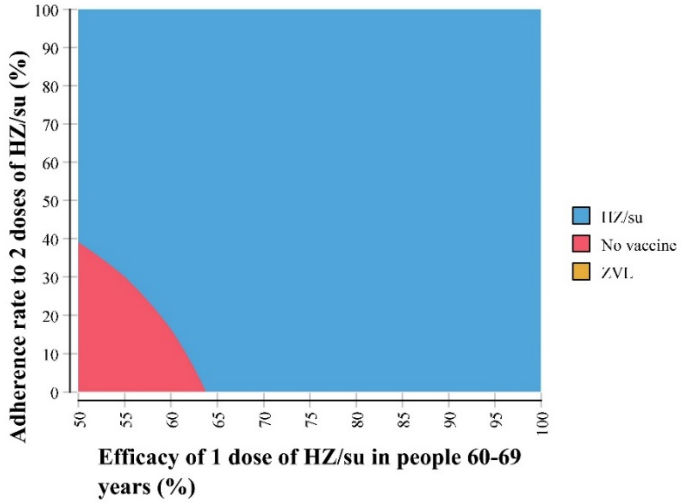


eFigure 1. Markov Model. HZ, Herpes zoster; ZVL, live attenuated varicella zoster vaccine; HZ/su, adjuvanted herpes zoster subunit vaccine; PHN, postherpetic neuralgia
1.a. Decision node and Markov states. The model begins with a decision node representing the choice to vaccinate with one of the vaccines, or no vaccine. For ZVL and no vaccine options, the cohort then moves to a chance node of male or female depending on the sex distribution of general population corresponding to the age of vaccination. After that, the cohort enters the Markov node and starts at the "Healthy" state for the first cycle. For subsequent cycles, they move between Markov health states depending on transition probabilities until everyone arrives in the "Dead" state, at which point the model terminates. For the HZ/su option, the cohort can receive 1 or 2 doses of the vaccine. The events afterwards are similar to those in the ZVL option.
1.b. Sub-tree. The sub-tree includes the chance events occurring within each annual Markov cycle. The details of the model sub-tree are available at
http://annals.org/data/Journals/AIM/934562/2ff6_Appendix_Figure_2_Markov_model_sub-tree.jpeg

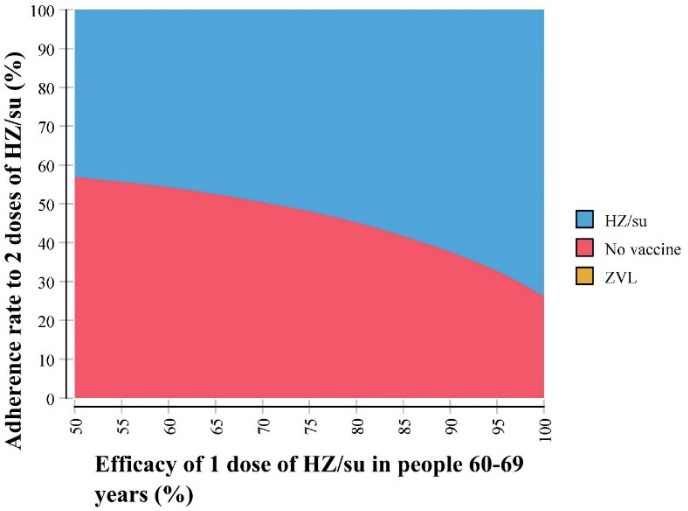
a. Waning rate of 1 dose double 2 doses (base-case)



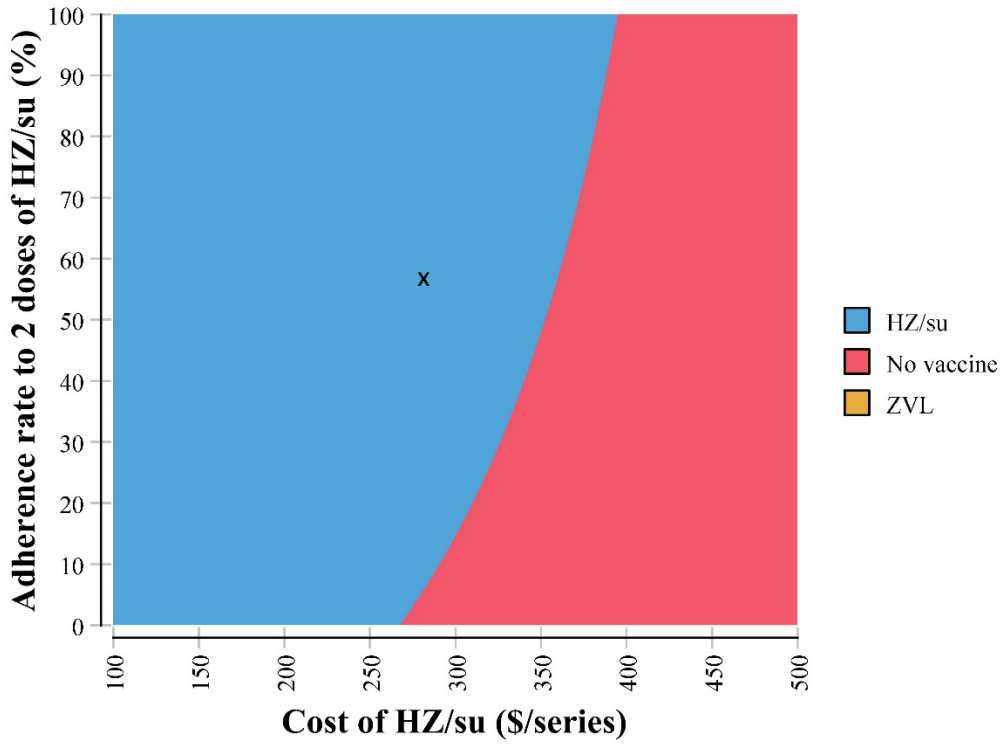
b. Waning rate of 1 dose equal 2 doses



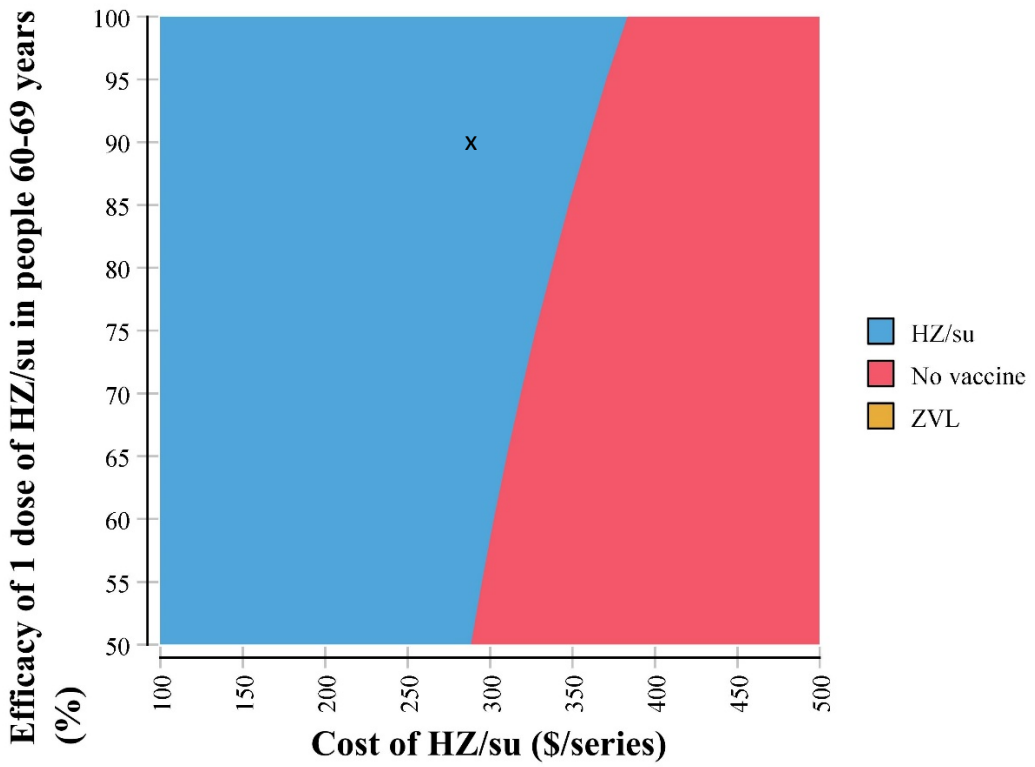
c. Waning rate of 1 dose triple 2 doses



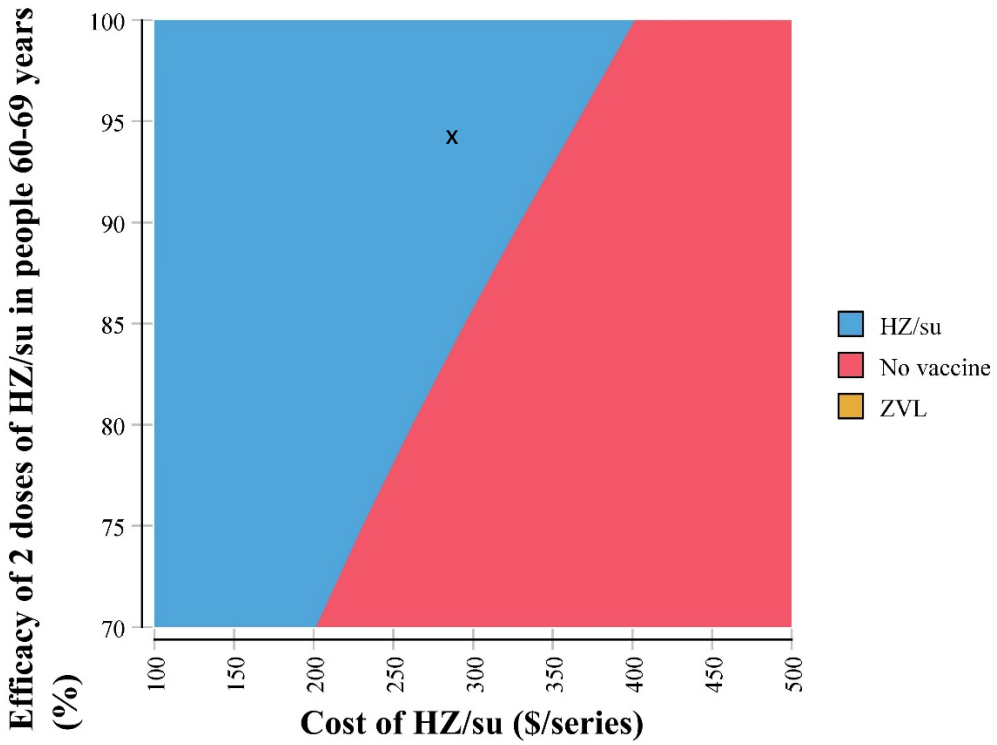
eFigure 2. Three-Way Sensitivity Analysis at Vaccination Age of 60 Years With a Willingness-to-Pay Threshold of $50,000/QALY. We varied adherence rate, efficacy and waning rate of a single dose of HZ/su at same time. HZ/su, adjuvanted herpes zoster subunit vaccine; ZVL, live attenuated varicella zoster vaccine.



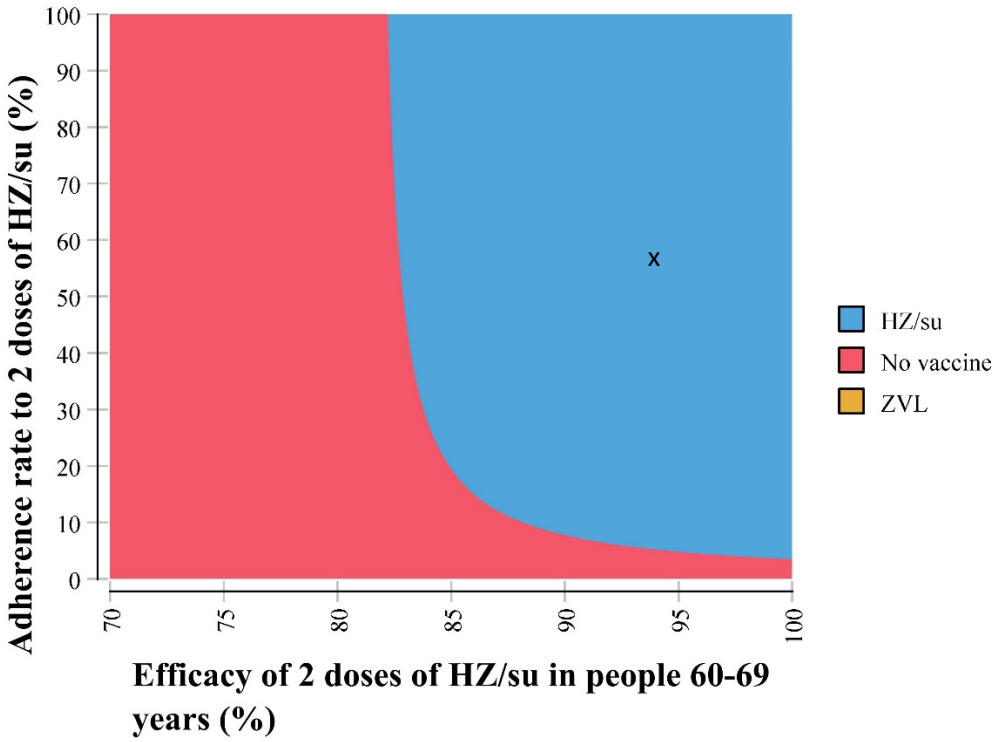
eFigure 3. Two-Way Sensitivity Analysis of Adherence Rate and Cost of HZ/su. This analysis was for people vaccinated at 60 years with a willingness-to-pay threshold of $50,000/QALY. HZ/su, adjuvanted herpes zoster subunit vaccine; ZVL, live attenuated varicella zoster vaccine.



eFigure 4. Two-Way Sensitivity Analysis of Efficacy of a Single Dose and Cost of HZ/su. This analysis was for people vaccinated at 60 years with a willingness-to-pay threshold of $50,000/QALY. HZ/su, adjuvanted herpes zoster subunit vaccine; ZVL, live attenuated varicella zoster vaccine.

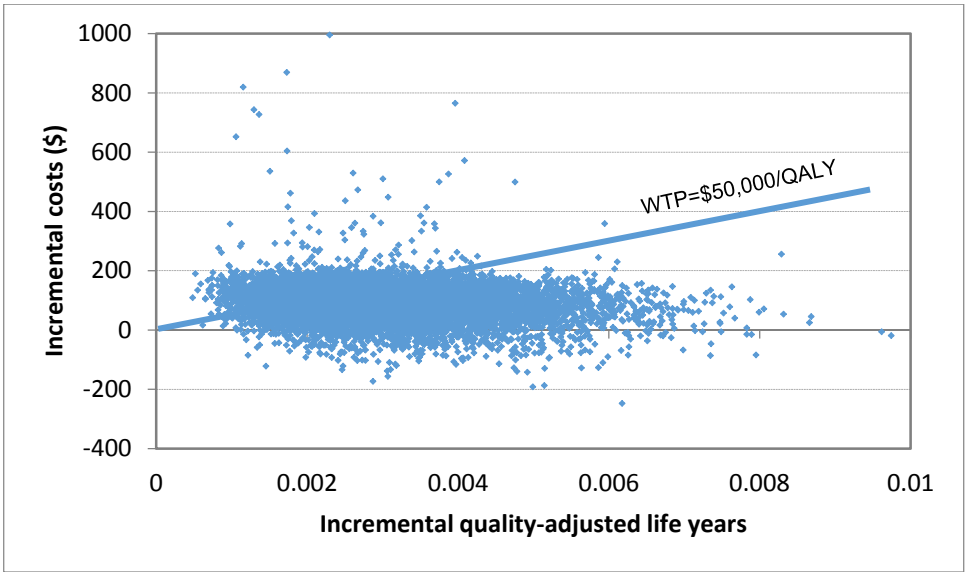


eFigure 5. Two-Way Sensitivity Analysis of Efficacy of Two Doses and Cost of HZ/su.
This analysis was for people vaccinated at 60 years with a willingness-to-pay threshold of $50,000/QALY. HZ/su, adjuvanted herpes zoster subunit vaccine; ZVL, live attenuated varicella zoster vaccine.



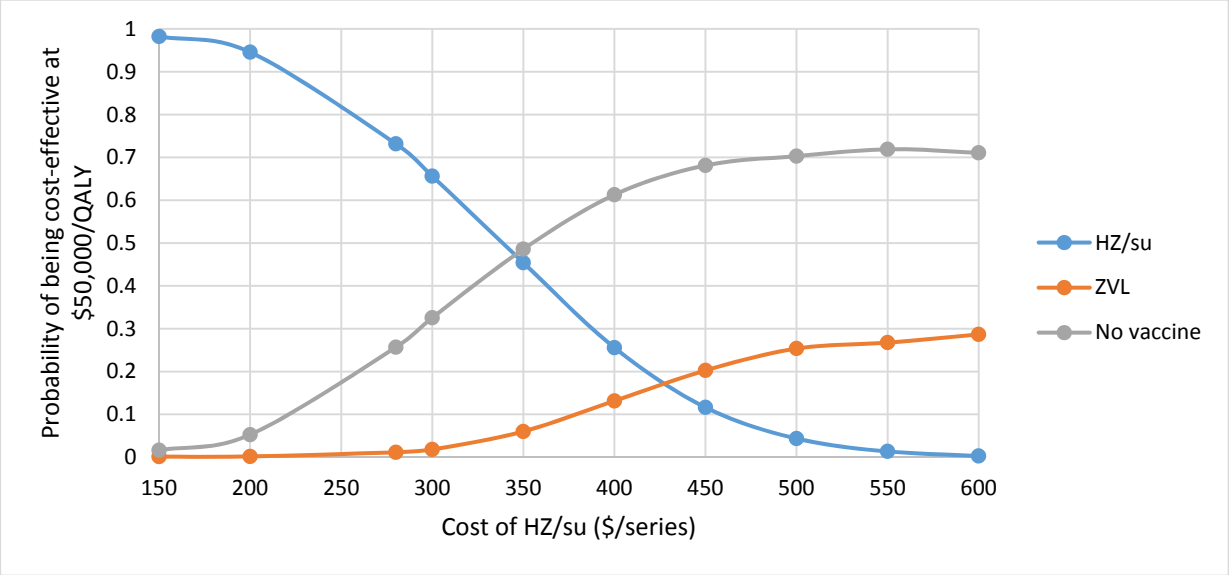
eFigure 6. Two-Way Sensitivity Analysis of Adherence Rate and Efficacy of Two Doses of HZ/su. This analysis was for people vaccinated at 60 years with a willingness-to-pay threshold of $50,000/QALY. HZ/su, adjuvanted herpes zoster subunit vaccine; ZVL, live attenuated varicella zoster vaccine.

a. HZ/su versus no vaccination



b. ZVL versus no vaccination

eFigure 7. Scatter Plot of Incremental Cost-effectiveness Ratios of the Adjuvanted Subunit Vaccine (HZ/su) (a) and Live Attenuated Vaccine (ZVL) (b) vs No Vaccination From Probabilistic Sensitivity Analysis in Person Vaccinated at 60 Years. The line represents the willingness-to-pay (WTP) threshold of $50,000/QALY. In this PSA, HZ/su price was assumed to be $280/2-dose course.



eFigure 8. The Probability of Being Cost-effective at $50,000/QALY of Each Strategy vs HZ/su Prices in People Vaccinated at 60 Years. HZ/su, adjuvanted subunit vaccine; QALY, quality-adjusted life year; ZVL, live attenuated herpes zoster vaccine.

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