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Cost-effectiveness of an Adjuvanted Recombinant Zoster Vaccine in older adults in the United States

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ABSTRACT

In the United States, herpes zoster (HZ) and related complications are estimated to result in approximately $1.3 billion in medical care costs and $1.7 billion in indirect costs annually. In this study, we compared the cost-effectiveness of a new Adjuvanted Recombinant Zoster Vaccine (RZV), containing recombinant varicella-zoster virus glycoprotein E and the $AS01_B$ Adjuvant System, versus No Vaccine, as well as versus the live attenuated HZ vaccine (Zoster Vaccine Live (ZVL)) in subjects aged 60+ years of age (YOA) and other age cohorts aged 50+ YOA. A multi-cohort Markov model was developed which follows 1 million individuals over their remaining lifetimes from the year of vaccination with annual cycle lengths. Second dose compliance for RZV was assumed to be 69%. Efficacy and waning parameters were derived from clinical trials for both vaccines. Epidemiological parameters, costs and utility model inputs were derived from US-specific population-based data. Costs and outcomes were discounted at 3% per year. Deterministic and probabilistic sensitivity analysis, along with scenario and threshold analysis were carried out to explore the overall uncertainty in the model. The model estimated that, compared to No Vaccine against HZ, RZV would prevent 103,603 HZ cases, 11,197 postherpetic neuralgia (PHN) cases, and 14,455 other complications, at an incremental cost of $11,863 per quality-adjusted life-year saved from a societal perspective. Compared to ZVL, the model estimated that, RZV would prevent 71,638 additional HZ cases, 6403 PHN cases, and over 10,582 other complications, resulting in net total societal cost savings of over $96 million. The results were robust to a wide range of sensitivity analyses. Vaccination against HZ with RZV is cost-effective compared to No Vaccine and cost-saving compared to ZVL, in the US population aged 60+ YOA.

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1. Introduction

Herpes zoster (HZ, shingles) is a viral infection elicited by the reactivation of varicella-zoster virus (VZV, chickenpox) [1]. The VZV-specific cellular immunity declines with aging, and the VZV can reactivate in later life to cause HZ [2]. HZ typically presents as an acute, painful, vesicular eruption distributed along a single dermatome. The acute pain may last for weeks evolving into postherpetic neuralgia (PHN), frequently defined as pain persisting or appearing 90 days after rash onset [3]. Other less frequent complications of HZ include ocular, neurological, and cutaneous complications [4–6]. HZ and its associated complications have a

Abbreviations: ACIP, Advisory Committee on Immunization Practices; AEs, adverse events; DSA, deterministic sensitivity analysis; HZ, shingles, Herpes zoster; RZV, Adjuvanted Recombinant Zoster Vaccine; ICER, incremental cost-effectiveness ratio; PHN, postherpetic neuralgia; PSA, probabilistic sensitivity analyses; QALY, quality-adjusted life-year; SPS, Shingles Prevention Study; US, United States; VE, vaccine efficacy; VZV, chickenpox, Varicella-Zoster Virus; YOA, years of age; ZEST, Zoster Efficacy and Safety Study; ZONA, ZOster ecoNomic Analysis; ZVL, Zoster Vaccine Live.

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significant negative impact upon patient quality of life with physical, psychological, social and functional health domains being greatly affected [7,8].

In the United States (US), 99.5% of the population 40+ years of age (YOA) have been infected with wild type VZV and are thus at risk of developing HZ [9]. It is estimated that, without an HZ vaccine, 30% of people will develop HZ during their lifetime [9].

HZ and related complications are estimated to result in approximately $1.3 billion in medical care costs and $1.7 billion in indirect costs annually [10]; and this burden is projected to rise substantially over the coming years due to the aging populations [11].

Since 2008, the Advisory Committee on Immunization Practices (ACIP) has recommended that adults aged 60+ YOA be vaccinated against HZ [12,13]. *Zostavax* (Zoster Vaccine Live [ZVL]) is currently approved for the prevention of HZ in individuals 50+ YOA [14]. It is a one-dose live-attenuated vaccine that utilizes the same Oka strain as in varicella vaccines but at a higher potency. The Adjuvanted Recombinant Zoster Vaccine (RZV, *Shingrix*) is a non-live subunit vaccine developed to be administered in a 2-dose schedule, as 2 doses produced a 3-fold higher glycoprotein E (gE)-specific cell mediated immune response than one dose. RZV combines gE, a protein found on the VZV that causes shingles, with an adjuvant system, $AS01_B$, which is intended to enhance the immunological response to the antigen [15]. Large clinical trials have been conducted for both vaccines. Whereas ZVL demonstrated efficacy results against HZ of 69.8% in individuals aged 50–59 YOA [16], decreasing to 37.6% in individuals aged 70+ YOA, RZV demonstrated efficacy results against HZ of 97.2% in subjects aged 50+ YOA and 91.3% in subjects aged 70+ YOA [15,17].

In 2017, RZV was approved in the US by the FDA [18]. The ACIP members subsequently recommended RZV vaccination: (1) in immunocompetent adults aged 50+ YOA, (2) in immunocompetent adults previously vaccinated with ZVL, and (3) preferred over ZVL [19]. The ACIP recommendations were made based on clinical efficacy data, health economic evidence, and immunogenicity data [19].

The analysis was conducted to address the primary research questions: "Is RZV cost-effective in US adults aged 60+ YOA who have never been vaccinated against HZ?" The cost-effectiveness analysis was carried out comparing RZV versus No Vaccine, as well as the HZ vaccine standard of care strategy in 2017 (i.e. versus ZVL).

2. Methods

2.1. Mathematical model

The ZOster ecoNomic Analysis (ZONA) model was developed in Microsoft Excel. It is a multi-cohort Markov model including five hypothetical cohorts split into age groups for people aged 50+ YOA (i.e. 50–59, 60–64, 65–69, 70–79, 80+). When considering vaccination scenarios, for example directed at ages 60+, the model assumes that all of the subjects in the 60–64, 65–69, 70–79 and 80+ age cohorts are vaccinated, as would occur in a 'catch-up' campaign. The model follows all subjects within a cohort over their remaining lifetimes from the year of vaccination with annual cycle lengths. Three different HZ vaccination strategies are compared: No Vaccine, vaccination with ZVL, and vaccination with RZV. Further details regarding the model structure are provided in the supplementary text and elsewhere [20].

2.2. Methodological assumptions

In the base-case analysis we evaluated the incremental cost-effectiveness ratio (ICER), in terms of cost per additional quality-adjusted life-year (QALY) gained, of vaccinating a cohort of 1 million individuals aged 60+ YOA in the age-specific US population. The primary perspective is that of the societal perspective, which includes both direct medical costs and indirect costs. Costs and outcomes are presented over the remaining lifetimes of individuals. Life years, QALYs, and costs were discounted at 3% per year.

2.3. Model inputs

Data for populating the model were taken from the published literature and national survey data sources. Further details are provided in the supplementary material text.

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.vaccine.2018.07.005.

US population sizes by age group were from the Census Bureau [21] and all-cause mortality rates (%) from Arias et al. [22].

Table 1 presents the epidemiological inputs applied in the base-case, sensitivity, and scenario analyses.

Supplementary text table 2 presents the overall vaccine efficacy (VE) against HZ and PHN for both ZVL and RZV. The VE for ZVL was from the Shingles Prevention Study (SPS) and Zoster Efficacy and Safety Study (ZEST) [16,23]. The persistence of VE against HZ for ZVL was modelled based on the data from the SPS and the subsequent persistence studies as presented by Morrison et al. [24]. Waning of VE for ZVL against HZ was estimated to be 5.4% per year during the first 4 years following vaccination and 5.1% thereafter. In the model, both the HZ and PHN year 1 VE estimates are based on adjusted overall study VE, i.e. the overall VE estimates, which were estimated over $\geq$3 years, are adjusted upwards to take into account the waning during the clinical trial follow-up period. The VE of RZV against HZ and PHN was taken from the ZOE-50 and ZOE-70 studies [15,17]. Further details are provided in the supplementary text. Based on the data from the clinical trials, it was assumed that for individuals aged 50–69 YOA receiving 2-doses of RZV, the HZ VE was assumed to wane at 1% annually during the first four years post-vaccination, 2.3% during the subsequent years until the age of 69, and 3.6% for all individuals aged 70+ YOA. In the absence of long-term VE data, we assumed that the VE for 1-dose of RZV against both HZ and PHN waned at the same rate as the VE of ZVL.

Coverage of the first dose for both vaccines was assumed to be 100%. We assumed that RZV doses were given two months apart. Compliance of the second dose of RZV was assumed to be 69% (range: 45–89%) in the base-case based on the vaccination series completion and compliance rates of hepatitis A and B among US adults [25].

The model also takes into account the incidence of adverse events (AEs) and medically attended visits which are potentially related to vaccination. These are described in detail in the supplementary text.

Table 2 presents the cost and utility inputs in the base-case, sensitivity, and scenario analyses. The RZV price per dose was assumed to be $140 with a range of $125–$175 used in deterministic sensitivity and scenario analysis. The ZVL price per dose was assumed to be $196.91 based on the private sector price per dose listed in the CDC Vaccine Price List [26]. The administration cost per dose was taken from Ortega-Sanchez [27], who reported $20 administration cost for ZVL (range $15–$50). A weighted cost of AEs related to vaccine administration for both RZV and ZVL was included in the model.

Baseline utility values for the US population were taken from Szende et al. [28]. QALY loss per HZ case by vaccination status and PHN status were reported in Pellissier et al. [29]. A weighted AE-related QALY loss per dose was calculated based on the proportion of subjects with a local/general reaction and the proportion with a serious event.

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Table 1
Model inputs: epidemiology parameters.

	Base value	Range	
		Lower bound	Upper bound
Epidemiology			
Annual HZ incidence			
50–59 YOA	0.00674	0.00539	0.00809
60–69 YOA	0.00932	0.00746	0.01350
70–79 YOA	0.01202	0.00962	0.01584
80+ YOA	0.01278	0.01022	0.01730
Source	[42]*	−20% of base value*	[43]*
Percentage of HZ cases with PHN (%)			
50–69 YOA	6.20%	4.96%	7.44%
70+ YOA	12.70%	10.16%	15.24%
Source	[17] and unpublished data	−20% of base value	+20% of base value
Annual recurrent HZ incidence			
50–59 YOA	0.00674	0.00110	0.00809
60–69 YOA	0.00932	0.00110	0.01350
70–79 YOA	0.01202	0.00143	0.01584
80+ YOA	0.01278	0.00143	0.01730
Source	[42,44]‡	[45]‡	[43]*,‡
Percentage of recurrent HZ cases with PHN (%)			
50–69 YOA	6.20%	3.72%	8.68%
70+ YOA	12.70%	7.62%	17.78%
Source	[17] and unpublished data	Double the range for initial HZ case PHN percentages	Double the range for initial HZ case PHN percentages
Case fatality rate for HZ cases			
50–59 YOA	0.0013%	0.0009%	0.0017%
60–69 YOA	0.0022%	0.0017%	0.0027%
70–74 YOA	0.0062%	0.0053%	0.0070%
75–79 YOA	0.0062%	0.0053%	0.0070%
80–84 YOA	0.0240%	0.0219%	0.0260%
85+ YOA	0.0734%	0.0688%	0.0778%
Source	[32]§	[32]§	[32]§
Complications			
Source	[6]#	[6]#	[6]#
Ocular			
50–59 YOA	2.87%	1.00%	4.71%
60–69 YOA	4.23%	1.00%	6.57%
70–79 YOA	4.53%	1.00%	6.94%
80+ YOA	6.91%	1.00%	10.08%
Neurological			
50–59 YOA	2.23%	0.60%	3.86%
60–69 YOA	3.17%	1.00%	5.21%
70–79 YOA	5.92%	1.00%	8.65%
80+ YOA	4.88%	1.00%	7.57%
Cutaneous			
50–59 YOA	1.59%	0.21%	2.98%
60–69 YOA	1.06%	0.00%	2.25%
70–79 YOA	2.09%	0.44%	3.75%
80+ YOA	2.85%	0.77%	4.92%
Other nonpain			
50–59 YOA	1.59%	0.21%	2.98%
60–69 YOA	1.41%	0.04%	2.78%
70–79 YOA	2.09%	0.44%	3.75%
80+ YOA	2.85%	0.77%	4.92%

HZ: herpes zoster; PHN: postherpetic neuralgia; YOA: years of age.

* Johnson et al. [42] reported incidence rates of HZ based on 2011 claims data (estimated using ICD-9-CM code 053.xx diagnoses) from the Truven Health Analytics MarketScan Commercial Claims and Encounters database and the Medicare Supplemental and Coordination of Benefits database. A range of -20% of the base incidence estimates for the lower bound was assumed; this was used instead of the published confidence intervals to represent greater uncertainty around HZ incidence. The upper bound estimates were taken from Tseng et al. [43], which reported incidence based on ICD-9 diagnoses of HZ for an unvaccinated and immunocompetent population of Kaiser Permanente members from 2007 to 2009; a weighted average was calculated between the reported incidence for ages 70–74 and 75–79 to derive the upper bound incidence for ages 70–79. Assumed +20% of base incidence for ages 50–59 as incidence for this age group was not reported in Tseng et al. [43].

‡ Recurrence rates assumed to be equal to HZ incidence rates based on Yawn et al. [44]. For the lower bound, we used values from Tseng et al. [45]; values were taken from the lower bound of the confidence intervals reported for recurrent HZ incidence in an unvaccinated cohort. The upper bound estimates were assumed to be the same as those for incidence of initial HZ.

§ Le and Rothberg [32] used CDC Wonder mortality data from 1999 to 2012 to determine case fatality from HZ. Case fatality percentage for 85+ YOA were calculated using case fatality percentages for 80–89 and 90+ YOA, weighted by population sizes from the US Census Bureau [21]. Published 95% confidence intervals from Le and Rothberg [32] were applied as the ranges.

Taken from Yawn et al. [6], in which they were based on a retrospective population-based study of the adult population of Olmsted County, Minnesota, from 1996 to 2001. 95% CI were derived based on a standard error that was calculated from the published data in Yawn et al. [6]. All lower bounds were set to a maximum of 1% for a more conservative lower bound estimate.

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Table 2
Model inputs: cost and utility parameters.

	Base value	Range	
		Lower bound	Upper bound
Direct medical costs			
Costs per HZ case			
Without PHN			
50–59 YOA	$876.40	$768.20	$984.61
60–69 YOA	$1065.48	$781.45	$1349.52
70–79 YOA	$1355.32	$1092.92	$1617.71
80+ YOA	$1355.32	$1092.92	$1617.71
Source	[41]	[41]*	[41]*
With PHN			
50–59 YOA	$2577.04	$2061.63	$3092.45
60–69 YOA	$5274.02	$4219.21	$6328.82
70–79 YOA	$5144.53	$4115.62	$6173.44
80+ YOA	$5144.53	$4115.62	$6173.44
Source	[41]	−20% of base value	+20% of base value
Costs per HZ-related complication			
Ocular	$3042.17	$2433.73	$3650.60
Neurological	$7213.61	$5770.89	$8656.34
Cutaneous	$7214.59	$5771.67	$8657.50
Other nonpain	$7623.38	$6098.70	$9148.05
Source	[41]	−20% of base value	+20% of base value
Indirect costs			
Lost productivity costs per HZ case¥			
50–59 YOA	$1689.17	$1259.68	$2118.65
60–64 YOA	$2269.10	$1636.24	$2901.96
65–69 YOA	$1220.51	$880.11	$1560.91
70–79 YOA	$455.19	$328.24	$582.15
80+ YOA	$313.05	$225.74	$400.36
Source	[46–48]	−20% of base value	+20% of base value
AE Cost			
Per RZV dose			
50–59 YOA	$24.08	$12.04	$48.16
60–64 YOA	$21.52	$10.76	$43.04
65–69 YOA	$21.05	$10.53	$42.10
70–79 YOA	$19.60	$9.80	$39.20
80+ YOA	$19.53	$9.77	$39.06
Source	See supplemental text for calculation	−50% of base value	+100% of base value
Per ZVL dose			
50–59 YOA	$13.42	$6.71	$26.84
60–64 YOA	$10.28	$5.14	$20.56
65–69 YOA	$10.01	$5.01	$20.02
70–79 YOA	$9.82	$4.91	$19.64
80+ YOA	$9.78	$4.89	$19.56
Source	See Supplemental text for calculation	−50% of base value	+100% of base value
Utility/QALY Loss			
Baseline Utility Values			
50–59 YOA	0.84120	0.83630	0.84610
60–64 YOA	0.82700	0.82110	0.83290
65–69 YOA	0.81300	0.80710	0.81890
70–79 YOA	0.78860	0.78190	0.79520
80+ YOA	0.75400	0.74620	0.76180
Source	[28]§	Derived from reported SE [28]	Derived from reported SE [28]
QALY loss per HZ case without PHN#			
Unvaccinated			
50–59 YOA	0.005	0.000	0.008
60–69 YOA	0.010	0.006	0.016
70+ YOA	0.012	0.007	0.018
Vaccinated			
50–59 YOA	0.005	0.000	0.007
60–69 YOA	0.010	0.006	0.014
70+ YOA	0.011	0.007	0.017
Source	[29]#	[29]#	[29]#
QALY loss per HZ case with PHN#			
Unvaccinated			
50–59 YOA	0.053	0.000	0.081
60–69 YOA	0.106	0.068	0.162
70+ YOA	0.156	0.100	0.233

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Table 2 (*continued*)

	Base value	Range	
		Lower bound	Upper bound
Vaccinated			
50–59 YOA	0.049	0.000	0.073
60–69 YOA	0.098	0.063	0.145
70+ YOA	0.091	0.058	0.136
Source	[29][#]	[29][#]	[29][#]

HZ: herpes zoster; PHN: postherpetic neuralgia; QALY: quality-adjusted life-year; RZV: Adjuvanted Recombinant Zoster Vaccine; AE: adverse events, SE: standard error; ZVL: Zoster Vaccine Live; YOA: years of age.

[*] For costs per HZ case without PHN, 95% confidence intervals were derived based on the reported standard errors in Yawn et al. [41].

[¥] It was assumed that hours lost per employed subject for 65+ YOA were the same of those for 60–64 YOA, as assumed in Le and Rothberg [32]. These work loss hours were multiplied by hourly wage estimates from the United States Bureau of Labor Statistics (BLS) [47] and were adjusted for employment percentage estimates by the BLS [48].

[§] For ages 50–59, calculated (in derivations sheet) a weighted average between the reported values for ages 45–54 and 55–64 YOA based on population estimates from the US Census Bureau [21]; the same approach was used for ages 70–79 YOA using reported values for ages 65–74 and 75+ YOA.

[#] QALY loss per HZ/PHN case were taken from Pellissier et al. [29]; for 50–59 YOA, no QALY loss was assumed for lower-bound estimates.

2.4. Sensitivity and scenario analyses

A deterministic sensitivity analysis (DSA) was conducted. The results of the DSA were summarized in a tornado diagram. A probabilistic sensitivity analyses (PSA) was conducted to consider the impact of the full uncertainty in model inputs and to explore the impact on the ICER of (a) RZV versus No Vaccine, and (b) RZV versus ZVL. The results of the PSA were presented on a cost-effectiveness plane and a cost-effectiveness acceptability curve.

Threshold analyses were conducted to investigate, for a selected set of key inputs, the values that those inputs could hold and still maintain ICER of RZV vs. No Vaccine below various willingness-to-pay hypothetical thresholds ranging from $0 to $160,000 per QALY gained.

We conducted two sets of scenario analyses, both comparing RZV with No Vaccine. In the first set, we varied the values of second-dose compliance for RZV, VE and waning of VE for RZV for 1 and 2 doses values, and weighted cost of AEs per vaccine dose; the scenarios are listed in Supplemental Text Table 5. In the second set, the ages targeted by the vaccine were changed to include adults aged 50+ YOA and then adults aged 65+ YOA. We also conducted an analysis presenting the ICER for the health sector perspective for the base-case age group including adults aged 60+ YOA, comparing RZV with No Vaccine.

Finally, we performed an analysis to answer the question: at which age did vaccination (i.e. 50, 60, 65, 70 and 80 YOA) yield the lowest ICER?

3. Results

The results of the base cost-effectiveness analysis of RZV versus No Vaccine and versus ZVL for a cohort of 1 million US adults aged 60+ YOA in the US are presented in Table 3. The model estimated that, compared to not vaccinating against HZ, RZV would prevent 103,603 HZ cases, 11,197 PHN cases and 14,455 other complications, over the remaining lifetimes of all individuals included in the model. This corresponds to approximately a 50% reduction in these outcomes. This reduced disease burden would result in a gain of 77 discounted life-years and 2291 discounted QALYs. The vaccination costs would total $304 million dollars, but the HZ cases prevented would save $208 million in direct costs and $68 million in indirect costs, resulting in a net total societal cost of vaccinating that cohort of 1 million adults of approximately $27.2 million. These outcomes equate to a net cost of $11,863 per QALY gained. Compared to ZVL, the model estimated that RZV would prevent 71,638 additional HZ cases, 6403 PHN cases, 10,582 other complications, and 13 HZ-related deaths. This reduced disease burden would result in a gain of 62 discounted life-years and 1261

Table 3
Base analysis results for 1 million US adults aged 60+ YOA vaccinated with No Vaccine, RZV or ZVL.

Outcome	No Vaccine	RZV	ZVL	RZV vs No Vaccine	RZV vs ZVL
Health outcomes					
HZ cases	196,063	92,460	164,098	(103,603)	(71,638)
PHN cases	22,580	11,382	17,785	(11,197)	(6403)
Complication cases	29,277	14,822	25,404	(14,455)	(10,582)
Ocular	10,688	5473	9263	(5215)	(3790)
Neurological	9789	4753	8395	(5037)	(3642)
Cutaneous	4337	2288	3841	(2049)	(1553)
Other nonpain	4463	2308	3905	(2155)	(1597)
HZ-related deaths	45	31	43	(14)	(13)
Costs (discounted)					
Vaccination costs	$0	$304,405,178	$226,897,269	$304,405,178	$77,507,909
Direct costs due to HZ	$371,165,848	$162,208,952	$300,362,422	($208,956,896)	($138,153,470)
Indirect costs due to HZ	$96,081,531	$27,815,584	$63,215,653	($68,265,947)	($35,400,069)
Total direct costs	$371,165,848	$466,614,130	$527,259,691	$95,448,282	$60,645,562
Total societal costs	$467,247,379	$494,429,714	$590,475,344	$27,182,335	($96,045,630)
Life-years/QALYs (discounted)					
Life-years	12,890,617	12,890,694	12,890,632	77	62
QALYs	10,119,612	10,121,903	10,120,642	2291	1261
Cost-effectiveness					
Incremental cost per QALY gained	–	–	–	$11,863	Cost saving

–: not applicable; HZ: herpes zoster; PHN: postherpetic neuralgia; QALY: quality-adjusted life-year; US: United States; YOA: years of age; ZVL: Zoster Vaccine Live; RZV: Adjuvanted Recombinant Zoster Vaccine; () refers to savings.

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discounted QALYs. The incremental vaccination costs would total almost $78 million dollars, but the HZ cases prevented would save $138 million in direct costs and over $35 million in indirect costs, resulting in net total societal cost savings of vaccinating that cohort of 1 million adults with RZV of approximately $96 million. The number needed to vaccinate to prevent one HZ cases was estimated to be 10 for RZV and 32 for ZVL.

The results of the DSA for the analysis of RZV versus No Vaccine for US adults aged 60+ YOA are presented in Fig. 1. The tornado diagram shows that the ICER was most sensitive to the following inputs based on their defined ranges: (i) annual waning of VE for RZV (one-dose and two-dose for all ages pooled), (ii) annual incidence of initial HZ, (iii) discount rate for costs and health outcomes pooled, (iv) annual waning of RZV (two-dose) efficacy for 70+ YOA, and (v) discount rate for costs. The highest ICER (or least cost-effective value) was observed when the annual waning of VE for RZV was at its upper bound ($63,858 per QALY gained). The majority (72%) of individual (versus grouped) inputs did not shift the ICER by more than $5000 in either direction.

The results of the PSA for the RZV versus No Vaccine analysis are presented in Fig. 2 and Supplementary Text Fig. 3. Approximately 98% of simulations and 99.5% of simulations resulted in costs per QALY gained by RZV versus No Vaccine below thresholds of $80,000 and $100,000, respectively. Results of the PSA for the RZV versus ZVL are presented in Fig. 2. 99% of simulations resulted in cost savings from RZV when compared with ZVL.

The results of the threshold analyses for RZV versus No Vaccine are presented in Fig. 3. The model estimated that the initial efficacy of RZV for 2 doses could be roughly 30% lower than the base-case (much lower than the lower bound of the 95% confidence interval observed in the clinical trial results) and still result in an ICER of RZV versus No Vaccine less than a threshold of $80,000 per QALY. Similarly, the model estimated that incidence of initial HZ could be about 30% less than base-case estimates and still result in ICERs of less than a threshold of $70,000 per QALY. This analysis also showed that while waning of RZV efficacy remained lower than 1.5 and 2 times as much as the base-case estimates, the ICER did not exceed $50,000 and $100,000, respectively. ICERs were less sensitive to changes in the weighted AE cost per RZV dose from base estimates; as a result, ICERs stayed below a $100,000 threshold until costs were almost 7 times higher (582% increase) than base values. The model estimated that the QALY loss inputs could be 60% and 80% lower than the base-case and still result in an ICER of RZV versus No Vaccine less than a threshold of $50,000 and $100,000 per QALY, respectively.

The results of the first set of scenario analyses for RZV versus No Vaccine for US adults aged 60+ YOA are presented in Supplemental Text Table 5. They show that the cost-effectiveness of using RZV to

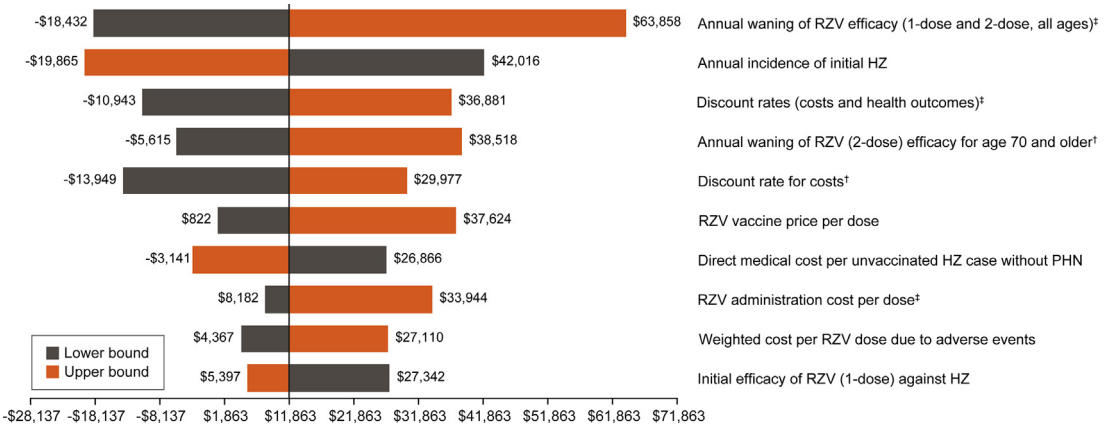

Fig. 1. DSA results for ICER of RZV vs No Vaccine for US adults aged 60+ YOA (Top 10). †: Individual variation of an input that is also varied in this DSA grouped with other potentially correlated inputs. Those groups are marked by a "‡" footnote; ‡: Group variation of a set of potentially correlated inputs, each of which is also varied in this DSA individually. Those inputs, when varied individually, are marked by a "†" footnote.
DSA: deterministic sensitivity analysis; HZ: herpes zoster; ICER: incremental cost-effectiveness ratio; PHN: postherpetic neuralgia; QALY: quality-adjusted life-year; RZV: Adjuvanted Recombinant Zoster Vaccine; US: United States; YOA: years of age.

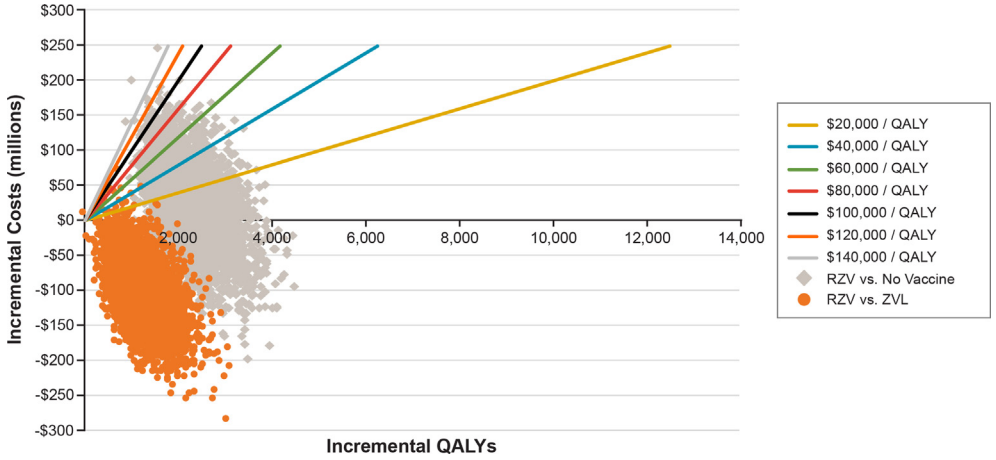

Fig. 2. Incremental costs vs. incremental QALYs from 5000 PSA simulations for each comparison, for US adults aged 60+ YOA.
PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life-year; RZV: Adjuvanted Recombinant Zoster Vaccine; ZVL: Zoster Vaccine Live; US: United States.

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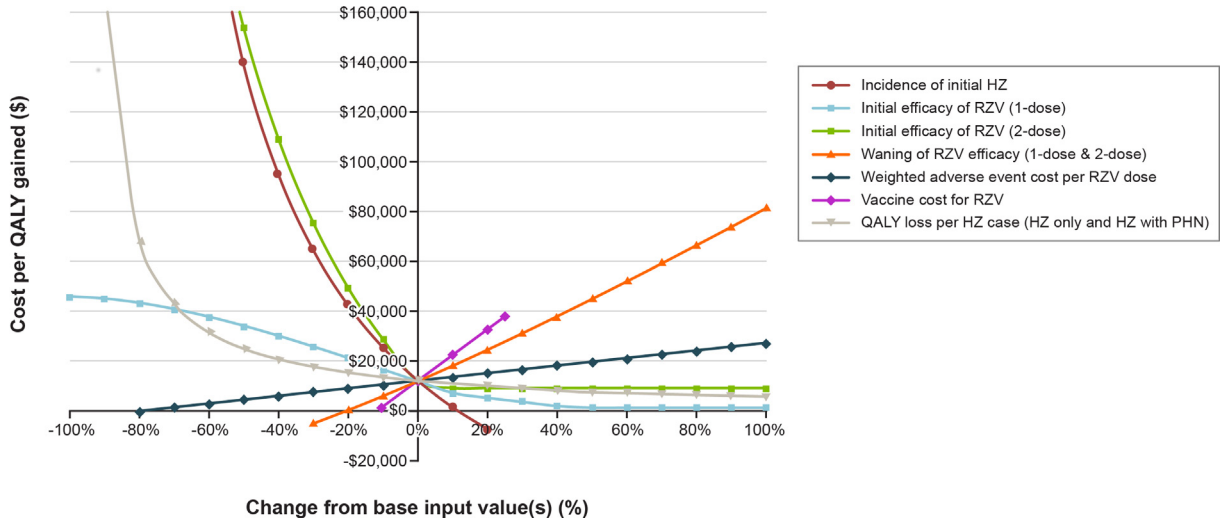

Fig. 3. Threshold Analysis: ICER for RZV vs. No Vaccine for US adults aged 60+ YOA across ranges of values for key inputs.
Note: Horizontal lines at varied cost-per-QALY values represent different hypothetical willingness-to-pay thresholds. HZ: herpes zoster; ICER: incremental cost-effectiveness ratios; PHN: postherpetic neuralgia; QALY: quality-adjusted life-year; RZV: Adjuvanted Recombinant Zoster Vaccine; US: United States; YOA: years of age.

vaccinate US adults aged 60+ YOA was robust to multiple combinations of unfavorable values for RZV for several of the key inputs. In the second set of scenario analyses, comparing RZV versus No Vaccine for vaccinating US adults aged 50+ YOA and 65+ YOA, the model estimated ICERs of $12,617 and $22,616 per QALY gained, respectively. In the analysis from the health sector perspective, comparing RZV versus no vaccine for vaccinating US adults aged 60+ YOA, the model estimated an ICER of $38,867 per QALY gained.

The model demonstrated that vaccinating with RZV was cost effective compared to No Vaccine for all ages investigated (i.e. 50, 60, 65, 70 and 80 YOA). Vaccinating with RZV at age 60 YOA would lead to cost savings while vaccinating at age 50 would yield an ICER of $14,916, compared with $4594, $20,383 and $56,143 at the ages 65, 70 and 80 YOA, respectively.

4. Discussion

In this study we presented the cost-effectiveness of RZV compared to either No Vaccine or ZVL for vaccinating US adults aged 60+ YOA against HZ. It was demonstrated that the RZV vaccine would be cost-effective compared to a No Vaccine strategy and cost-saving compared to ZVL vaccination. One of the strengths of our model is that it is quite consistent with respect to inputs and outcomes compared with an independently developed model and the CDC model presented at ACIP [30,34,40]. Some differences existed in terms of waning inputs, as described below, and QALY inputs, i.e. the ZONA model assumed smaller QALY (utility) loss input values compared to the other models. In our study, although there is considerable uncertainty in many of the parameters, the results were robust to a variety of sensitivity and scenario analyses.

A recent literature review of ZVL cost-effectiveness studies reported diverging results [3]. The authors reported that the results were largely influenced by assumptions regarding duration of vaccine protection, inclusion of VE on PHN in patients who developed HZ, and a loss in quality of life associated with HZ and PHN. In 2007, two key studies were published reporting the cost-effectiveness of vaccinating US adults with ZVL using VE estimates from the SPS trial [29,31]. While Pellisier et al. [29] assumed no waning of VE in the base case analysis, Rothberg assumed a logarithmic waning function [31]. More recent analyses of cost-effectiveness of ZVL assumed waning of vaccine protection against HZ based on data from the Long Term Persistence Study [13,24,32,33]. For example, in the model by Hales et al. [13] VE against herpes zoster for ZVL was assumed to wane to 0 over 10 years.

The DSA results in this paper also suggested that the cost-effectiveness of RZV versus No Vaccine was sensitive to assumptions regarding the waning of efficacy, in particular for waning of RZV 2-dose efficacy for subjects aged 70+ YOA. Dooling et al. [19], when describing the waning rates of both vaccines, reported that vaccine effectiveness for ZVL "wanes substantially over time" whereas for RZV "modest waning of protection over 4 years following vaccination" was observed [19]. A model by Le and Rothberg assumed that vaccine efficacy of RZV 2-dose and ZVL would wane at the same rates (5.4% per year) [34]. The authors concluded that their assumptions were conservative, as did Najafzadeh [35], who reported that Le and Rothberg [34] used "a conservative assumption that the RZV efficacy rate declines as fast as ZVL efficacy did, which is likely a cautious assumption" [34,35].

In the ZONA model, efficacy and waning assumptions, based on clinical trial data, for both HZ vaccines were validated by a panel of international experts in September 2016. The design of the ZOE studies was very close to the SPS study. Some differences did exist, in particular with respect to age groups participating, and while the SPS study included US sites only, the ZOE studies were conducted in 18 countries worldwide. For RZV 2-doses, waning was estimated to be 1% (95% confidence intervals 0–2.6%) and 3.6% (95% confidence intervals 1.4–6.6%) in the ZOE-50 and ZOE-70 pooled analysis respectively [20]. These values were extrapolated as inputs in the model. In the meantime, results of a phase IIIB, open-label study following participants who had received two doses of RZV for up to 9 years after the first dose to determine the persistence of the immune response have become available [36]. Although both cell-mediated immunity and humoral immune responses to RZV decreased initially over time, both levelled off at around 4 years post-vaccination and remained stable, well above baseline, for 9 years in adults 60+ YOA.

Wide ranges of values were considered for both efficacy and waning of efficacy against HZ for RZV 1-dose. Compliance for the second dose of RZV was very high, i.e. approximately 95%, in both the ZOE-50 and ZOE-70 clinical trials, so there were limited efficacy data on individuals who received only 1 dose. Nevertheless,

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phase II clinical trial data suggest that the immune responses after a single-dose administration remain above the pre-vaccination baseline throughout month 36 [37]. The long-term immunogenicity data following a single dose administration regimen have been generated with a formulation which contained double the dose of gE, compared to RZV. However, given that the same study has shown that the immune responses two months following either a single dose of either 50μgE/AS01$_B$ or a single dose of 100μgE/AS01$_B$ are comparable, it is plausible to assume that the long-term data can be generally extrapolated to the RZV.

Utility losses for HZ cases were based on data for ZVL [29]. Pellisier et al. [29] reported that subjects vaccinated with ZVL who went on to develop HZ and PHN had reduced utility losses from HZ and PHN compared to unvaccinated subjects who also developed those conditions. Similar findings of reduced disease severity of breakthrough HZ episodes in subjects vaccinated with RZV were reported for the ZOE-50 and ZOE-70 trial analyses [38], suggesting that the use of the same utility values is reasonable for both HZ vaccines.

A limitation of this study is that efficacy data and HZ incidence data were based on immunocompetent individuals only. As efficacy data become available for RZV in immunocompromised individuals, additional cost-effectiveness analyses that consider immunocompromised populations should be carried out. Another limitation of the study is the uncertainty regarding real-life, multi-dose compliance in older adults. Nevertheless, a wide range of values were selected to reflect uncertainty regarding this parameter (i.e. 45–89%) [19,39]. The second-dose compliance was allowed to vary in DSA, PSA, and scenario analyses, which consistently showed that this parameter had little impact on the overall ICER.

As with the CDC model, presented at ACIP 2017, one additional limitation of our model was that many of the epidemiological and cost input parameters were based on a population based study in a single county in Minnesota [40,41].

Vaccination against HZ with RZV has been demonstrated to be efficacious in two randomized phase III clinical trials [15,17]. In this paper we have also shown that vaccination against HZ with RZV is cost-effective compared to No Vaccine and cost-saving compared to ZVL in the US population aged 60 YOA and over. This evidence provides additional information for clinicians, payers and policy makers, and may help in their assessment of the value of vaccination against HZ, in order to reduce the burden of disease in the US.

Trademark section

Shingrix is a trademark from the GSK group of companies.
Zostavax is a trademark from Merck Sharp & Dohme Corp.

Authors' contributions

DC, PB, BL, BP, DVO, LV and BY participated in the conception and design of the study. DC, JC, KH, BP, DVO and LV participated in the collection or generation of the study data. DC, PB, JC, KH, BP, DVO and LV performed the study. DC, PB, JC, KH, BL, BP and DVO contributed to the material. DC, PB, JC, KH, BL, BP, DVO, LV and BY were involved in the analysis or interpretation of the data. All named authors provided substantial intellectual and scientific input during the manuscript development, critically reviewing the content, revising the manuscript and giving final approval before submission. The work described was carried out in accordance with the ICMJE recommendations for conducting, reporting, editing and publishing scholarly work in medical journals. The work presented in the article has been carried out in an ethical way.

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Conflict of interest

DC, DVO, PB, BP and LV are employees of the GSK group of companies. DC, PB, and BP own stock options as part of their employee remuneration. BP reports personal fees and non-financial support from Pennsylvania Pharmacists Association (travel/lodging/services related to participation on the Pharmacy Practice Care Network Research Working Group). He reports personal fees from GSK where he is employed and received restricted stock. BY reports grants from GSK (paid to her institution), personal fees from GSK (HZ advisory board and as a consultant), grants from Merck (paid to her institution) and personal fees from Merck (HZ advisory board) outside the submitted work. BL received personal fees from GSK (paid as a consultant). He is member of the editorial board of Vaccine but did not participate to the editorial support or the final decision of this manuscript. JC's and KH's employer, RTI - Health Solutions, received funding via a contractual agreement with GSK to perform the work contributing to this research.

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