Projected Risks and Health Benefits of Vaccination against Herpes Zoster and Related Complications:

Interim Results

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Conflict of interest statement

Authors have no known conflicts of interest.

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.



Objective

 To evaluate the tradeoffs between benefits of averted cases of herpes zoster and complications and risks of potential adverse events, specifically Guillain-Barré syndrome



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Methods: Risk-Benefit Analysis

- Existing simulation model used to estimate health outcomes, incorporating new data on Guillain-Barré syndrome (GBS)
 - Model structure: state-transition cohort model (n=1,000,000)
 - Outcome measures: projected cases of herpes zoster (HZ), postherpetic neuralgia (PHN), complications, deaths, and GBS [no quality-adjusted life years (QALYs)]
 - Cycle length: annual
 - Model inputs: published evidence, primary data, expert opinion
 Prosser LA, et al. A cost-effectiveness analysis of vaccination for prevention of herpes zoster and related complications: input for national recommendations. *Ann Intern Med.* 2019;170(6):380-8.
- New data/revised assumptions
 - Health states added for GBS following HZ & GBS following vaccination with recombinant zoster vaccine (RZV); recurrent HZ excluded
 - 2-dose completion rate revised from 100% assumption in original analysis to 80-86%; 1-dose vaccine effectiveness (VE) updated
 - Unpublished data



Methods: Interventions

Strategies:

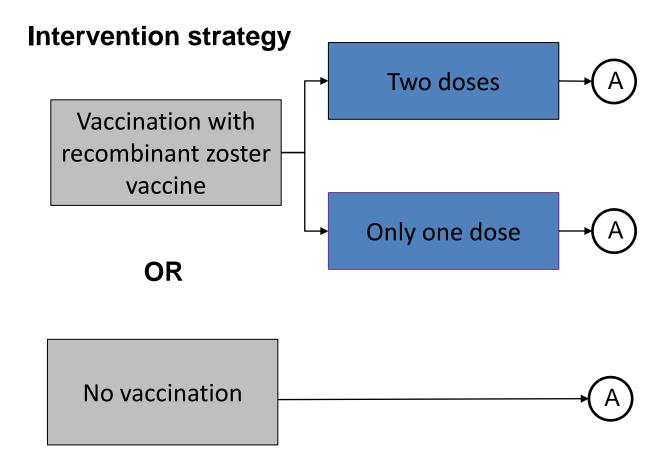
- 1. Vaccination with recombinant zoster vaccine (RZV)
- 2. No vaccination

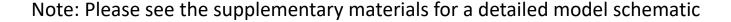
Assumptions:

- 5 age-based cohorts: 50-59, 60-69, 70-79, 80-89, 90-99
- Analytic time horizon was vaccination age through 20 years (10y, lifetime)
- 2-dose series completion rate: 80% for 50-64y and 86% for 65+y (base case)
- Discount rate: 1.5% (0, 3%)



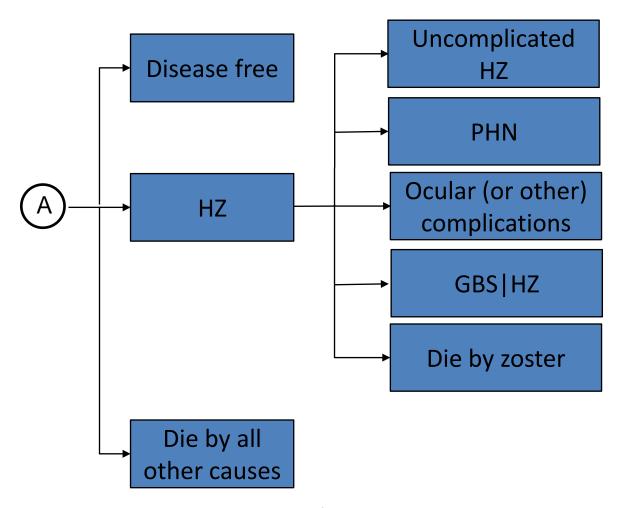
Methods: Simulation model (1)







Methods: Simulation model (2)



Note: Please see the supplementary materials for a detailed model schematic



Estimated probability of GBS associated with RZV

- VSD analysis, unpublished data (Nelson et al., presented ACIP, 10/2020)
 - Risk of GBS following RZV estimated using historical Zostavax (ZVL) comparator [3 cases in ZVL group: 1 unconfirmed)
 - Compared adverse event risks among 50-65 year-old RZV recipients (2018-2019)
 with 60-65 year-old ZVL vaccinees (2013-2017)
 - N = 647,307 doses
 - Incremental risk difference (pooled single-dose risk) per million doses
 - **2 confirmed cases**: 1.65 (-5.02, 8.33)
 - 3 confirmed cases: 0.16 (-7.12, 7.45)
- FDA safety study, unpublished data
 - Risk of GBS following RZV estimated using self-controlled case series approach;
 Medicare data
 - Extended Study Period/PPV-Adjusted attributable risk (10/2017-2/2020)
 - N = 1,318,004 doses
 - Attributable risk (pooled single-dose risk) per million doses: 3.13 (0.62, 5.64)



Estimated probability of GBS associated with RZV

Parameter	Most Likely	Lower Bound	Upper Bound	Source
GBS RZV	Pe	r 1,000,0	00*	
Pooled single dose risk (both doses)	1.65	0	8.33	VSD data • Conservative assumption
Dose 1 (single dose risk)**	3.30	0	13.6	 2 confirmed cases in ZVL comparator, IRD: 1.65 (-5.02, 8.33) Lower bound censored at zero; model cannot reflect "negative" cases;
2-dose series, combined risk**	3.30	0	13.6	distribution for this parameter is modeled as a 2-part function
Pooled single dose risk (both doses)	3.13	0.62	5.64	 FDA safety study AR for 2-dose series derived as 2x the pooled single-dose risk; dose 1 specific
Dose 1 (single dose risk)	6.48	3.36	9.60	risk applied for individuals who do not complete 2-dose series • Study reports 0.22 rate ratio for 2 nd -dose
2-dose series, combined risk**	6.26	1.24	11.3	specific analysis – "protective effect" – consistent with lower estimated risk for 2-dose series

^{*}Vaccinated (per million doses for single dose risks; per million vaccinated for the 2-dose series)

GBS=Guillain-Barré syndrome; RZV= Recombinant zoster vaccine; ZVL= Zoster vaccine live



^{**}Assumption

New input parameters for GBS | HZ

- New health state added to model to estimate GBS following HZ
- Probability of GBS following HZ (unadjusted attributable risk estimates calculated using data from Anderson et al, under review)

Parameter	Most	Lower	Upper	Source
T draineter	Likely	Bound	Bound	354160
GBS HZ	Per m	illion HZ ep	isodes	
18-64y	8.6	1.3	33.9	IBM MarketScan® data
				Anderson et al., under review
65+y	12.8	3.7	31.9	CMS Medicare data
				Anderson et al., under review

HZ= Herpes zoster; GBS=Guillain-Barré syndrome



Analysis Plan

- Base case analysis
- Uncertainty analyses
 - Probabilistic analysis
 - One-way sensitivity analyses, including time horizon, discount rate
 - Multi-way sensitivity analyses
- Best-case/worst-case analysis



Summary base case results, projected cases

20 year time horizon, discounted

			HZ (case	es per million) †		
Age group	Strategy	trategy Cases Uncomplicated		Cases Ocular Complications	Deaths	Total HZ (cases +deaths)
50-59 years	Not vaccinated	87,173	12,562	9,871	110	109,681
	Vaccinated - RZV	49,578	7,038	5,505	62	62,284
60-69 years	Not vaccinated	98,034	19,211	11,609	129	128,984
	Vaccinated - RZV	51,387	9,861	6,604	67	67,380
70-79 years	Not vaccinated	88,131	22,350	10,959	329	121,771
	Vaccinated - RZV	42,756	10,412	5,274	158	58,600
80-89 years	Not vaccinated	61,355	19,148	7,986	240	88,730
	Vaccinated - RZV	21,581	6,728	2,808	84	31,202
90-99 years	Not vaccinated	35,907	13,650	4,916	147	54,621
	Vaccinated - RZV	7,735	2,897	1,055	32	11,719

[†] Cases per cohort. Each cohort includes 1 million individuals some proportion of whom experience HZ and some who do not. For example, for unvaccinated individuals 60-69 y, this includes 128,984 total cases HZ and 871,016 individuals without HZ, over the 20 year time horizon.



HZ= Herpes zoster; PHN= Postherpetic neuralgia; RZV= Recombinant zoster vaccine

Summary base case results, w/ cases of GBS

20 year time horizon, discounted

				HZ (cases per million) †						
Age group	Strategy	Cases GBS RZV* (VSD)	Cases GBS RZV* (FDA)	Cases Uncomplicated	Cases PHN	Cases Ocular Complications	Deaths	Cases GBS	Total HZ (cases +deaths)	
50-59 years	Not vaccinated Vaccinated - RZV	- 3.3	- 6.3	87,173 49,578	12,562 7,038	9,871 5,505	110 62	0.9 0.5	109,681 62,284	
60-69 years	Not vaccinated Vaccinated - RZV	- 3.3	- 6.3	98,034 51,387	19,211 9,861	11,609 6,604	129 67	1.4 0.7	128,984 67,380	
70-79 years	Not vaccinated Vaccinated - RZV	3.3	- 6.3	88,131 42,756	22,350 10,412	10,959 5,274	329 158	1.6 0.8	121,771 58,600	
80-89 years	Not vaccinated Vaccinated - RZV	3.3	- 6.3	61,355 21,581	19,148 6,728	7,986 2,808	240 84	1.1 0.4	88,730 31,202	
90-99 years	Not vaccinated Vaccinated - RZV	3.3	- 6.3	35,907 7,735	13,650 2,897	4,916 1,055	147 32	0.7 0.2	54,621 11,719	

^{*}Cases per million RZV vaccinated (1 dose or 2-dose series)

2/25/21

[†] Cases per cohort. Each cohort includes 1 million individuals some proportion of whom experience HZ and some who do not. For example, for unvaccinated individuals 60-69 y, this includes 128,984 total cases HZ and 871,016 individuals without HZ, over the 20 year time horizon.

HZ= Herpes zoster; PHN= Postherpetic neuralgia; GBS=Guillain-Barré syndrome; RZV= Recombinant zoster vaccine

Summary base case results, cases & cases averted

20 year time horizon, discounted, 60-69y

			Cases HZ (per million) †						
Strategy	GBS RZV*	GBS RZV*	Cases Uncomplicated	Cases PHN	Cases Ocular Complications	Deaths	Cases GBS	Total HZ	
Vaccinated - RZV	- 3.3 3.3	- 6.3 6.3	98,034 51,387 (46,648)	19,211 9,861 (9,350)	11,609 6,604 (5,544)	129 67 (62)	1.4 0.7 (0.7)	128,984 67,380 (61,604)	
	Strategy Not vaccinated Vaccinated - RZV Incremental	Not vaccinated - Vaccinated - RZV 3.3	Strategy GBS RZV* (VSD) GBS RZV* (FDA) Not vaccinated Vaccinated - RZV 3.3 6.3	Strategy GBS RZV* (VSD) GBS RZV* (FDA) Cases Uncomplicated Not vaccinated 98,034 Vaccinated - RZV 3.3 6.3 51,387	Cases Chicomplicated Cases PHN	Strategy Cases GBS RZV* (VSD) Cases GBS RZV* (FDA) Cases Uncomplicated Cases PHN Cases Ocular Complications Not vaccinated Vaccinated - RZV - - 98,034 51,387 19,211 9,861 11,609 6,604	Cases Complications Deaths	Cases Cases Cases Cases Cases Cases Cases Complicated Cases Cases Complications Cases Cases Cases Complications Cases Cases	

^{*}Cases per million RZV vaccinated (1 dose or 2-dose series)

HZ= Herpes zoster; PHN= Postherpetic neuralgia; GBS=Guillain-Barré syndrome; RZV= Recombinant zoster vaccine

 $^{2}/^{25}/^{21}$

[†] Cases per cohort. Each cohort includes 1 million individuals some proportion of whom experience HZ and some who do not. For example, for unvaccinated individuals 60-69 y, this includes 128,984 total cases HZ and 871,016 individuals without HZ, over the 20 year time horizon.

Summary base case results, cases & cases averted

20 year time horizon, discounted, all age groups

					C	ases HZ (per m	illion) †		
Age group	Strategy	Cases GBS RZV* (VSD)	Cases GBS RZV* (FDA)	Cases Uncomplicated	Cases PHN	Cases Ocular Complications	Deaths	Cases GBS	Total HZ
50-59 years	Not vaccinated Vaccinated - RZV Incremental	3.3 3.3	- 6.3 6.3	87,173 49,578 (37,559)	12,562 7,038 (5,524)	9,871 5,505 (4,266)	110 62 (47)	0.9 0.5 (0.4)	109,681 62,284 (47,397)
60-69 years	Not vaccinated	-	-	98,034	19,211	11,609	129	1.4	128,984
	Vaccinated - RZV	3.3	6.3	51,387	9,861	6,604	67	0.7	67,380
	Incremental	3.3	6.3	(46,648)	(9,350)	(5,544)	(62)	(0.7)	(61,604)
70-79 years	Not vaccinated	-	-	88,131	22,350	10,959	329	1.6	121,771
	Vaccinated - RZV	3.3	6.3	42,756	10,412	5,274	158	0.8	58,600
	Incremental	3.3	6.3	(45,375)	(11,938)	(5,685)	(171)	(0.8)	(63,170)
80-89 years	Not vaccinated	-	-	61,355	19,148	7,986	240	1.1	88,730
	Vaccinated - RZV	3.3	6.3	21,581	6,728	2,808	84	0.4	31,202
	Incremental	3.3	6.3	(39,774)	(12,421)	(5,178)	(155)	(0.7)	(57,528)
90-99 years	Not vaccinated	-	-	35,907	13,650	4,916	147	0.7	54,621
	Vaccinated - RZV	3.3	6.3	7,735	2,897	1,055	32	0.2	11,719
	Incremental	3.3	6.3	(28,171)	(10,753)	(3,861)	(116)	(0.5)	(42,902)

^{*}Cases per million RZV vaccinated (1 dose or 2-dose series)

2/25/21

[†] Cases per cohort. Each cohort includes 1 million individuals some proportion of whom experience HZ and some who do not. For example, for unvaccinated individuals 60-69 y, this includes 128,984 total cases HZ and 871,016 individuals without HZ, over the 20 year time horizon. HZ= Herpes zoster; PHN= Postherpetic neuralgia; GBS=Guillain-Barré syndrome; RZV= Recombinant zoster vaccine

Projected incremental cases GBS & averted cases HZ

20 year time horizon, discounted

					Averted Cases HZ (per million) †							
Age group	Age group Strategy GBS RZV* (VSD)	Cases GBS RZV* (FDA)	Uncomplicated	PHN	Ocular Complications	Deaths	GBS	Total HZ				
50-59 years	Vaccinated	3.3	6.3	(37,559)	(5,524)	(4,266)	(47)	(0.4)	(47,397)			
60-69 years	Vaccinated	3.3	6.3	(46,648)	(9,350)	(5,544)	(62)	(0.7)	(61,604)			
70-79 years	Vaccinated	3.3	6.3	(45,375)	(11,938)	(5,685)	(171)	(0.8)	(63,170)			
80-89 years	Vaccinated	3.3	6.3	(39,774)	(12,421)	(5,178)	(155)	(0.7)	(57,528)			
90-99 years	Vaccinated	3.3	6.3	(28,171)	(10,753)	(3,861)	(116)	(0.5)	(42,902)			

^{*}Incremental cases per million RZV vaccinated (1 dose or 2-dose series)

HZ= Herpes zoster; PHN= Postherpetic neuralgia; GBS=Guillain-Barré syndrome; RZV= Recombinant zoster vaccine

[†] Cases per cohort. Each cohort includes 1 million individuals some proportion of whom experience HZ and some who do not. For example, for unvaccinated individuals 60-69 y, this includes 128,984 total cases HZ and 871,016 individuals without HZ, over the 20 year time horizon.

Probabilistic sensitivity analysis

20 year time horizon, discounted, 60-69 years Base case values (95% CI)

Age group	Strategy	Cases GBS RZV (per million)	Cases GBS HZ (per million)	Total, GBS HZ and GBS RZV (per million)	Incremental total GBS cases, (per million)†
60-69y	Not vaccinated	-	1.4 (0.3; 3.3)	1.4 (0.3; 3.3)	-
(VSD)	Vaccinated-RZV	3.3 (0.0; 12.7)	0.7 (0.1; 1.6)	4.0 (0.2; 13.3)	2.6 (-1.6, 11.8)
60-69 y	Not vaccinated	-	1.4 (0.3;3.3)	1.4 (0.3; 3.3)	-
(FDA)	Vaccinated-RZV	6.3 (2.0; 10.6)	0.7 (0.1; 1.6)	7.0 (2.5; 11.3)	5.6 (1.2, 9.9)



Projected incremental cases GBS & averted cases HZ

20 year time horizon, discounted

		Incr.	Incr.	Ave	HZ (per mil	Z (per million)†		
Age group	Strategy	Cases GBS (VSD)*	Cases GBS (FDA)*	Uncomplicated	PHN	Ocular Complica- tions	Deaths	Total HZ
50-59 y	Vaccinated	2.9	5.9	(37,559)	(5,524)	(4,266)	(47)	(47,397)
60-69 y	Vaccinated	2.6	5.6	(46,648)	(9,350)	(5,544)	(62)	(61,604)
70-79 y	Vaccinated	2.5	5.5	(45,375)	(11,938)	(5,685)	(171)	(63,170)
80-89 y	Vaccinated	2.6	5.6	(39,774)	(12,421)	(5,178)	(155)	(57,528)
90-99 y	Vaccinated	2.8	5.7	(28,171)	(10,753)	(3,861)	(116)	(42,902)

^{*}Cases per million RZV vaccinated (1 dose or 2-dose series)

HZ= Herpes zoster; PHN= Postherpetic neuralgia; GBS=Guillain-Barré syndrome; RZV= Recombinant zoster vaccine

[†] Cases per cohort. Each cohort includes 1 million individuals some proportion of whom experience HZ and some who do not. For example, for unvaccinated individuals 60-69 y, this includes 128,984 total cases HZ and 871,016 individuals without HZ, over the 20 year time horizon.

Limitations

- Reliance on unpublished data for key parameters
- Limited data available
- Challenges of characterizing rare events
- Quality-adjusted life years not included



Summary

- Evaluated tradeoffs between benefits of averted cases of HZ and complications and risks of rare adverse events
- Estimated outcomes per 1,000,000 vaccinated individuals
 - Averted cases of HZ, PHN, other complications (e.g., GBS), and deaths
 - Rare adverse events (e.g., GBS)
- Projected cases of GBS are sensitive to parameter uncertainty
- Estimates of averted cases of HZ, complications, and deaths rely on published data and less sensitive to changes in parameter inputs

