Cost-effectiveness of adult vaccination strategies using pneumococcal conjugate vaccine compared with pneumococcal polysaccharide vaccine

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Abstract

Context—The cost-effectiveness of 13-valent pneumococcal conjugate vaccine (PCV13) compared with 23-valent pneumococcal polysaccharide vaccine (PPSV23) among US adults is unclear.

Objective—To estimate the cost-effectiveness of PCV13 vaccination strategies in adults to assist vaccination policy decision-making.

Design, Setting, and Population—A Markov state-transition model, lifetime time horizon, societal perspective. Simulations were performed in hypothetical cohorts of US 50-year-olds. Vaccination strategies and effectiveness estimates were developed by a Delphi expert panel; indirect (herd immunity) effects resulting from childhood PCV13 vaccination were extrapolated based on observed PCV7 effects. Data sources for model parameters included CDC Active Bacterial Core surveillance, National Hospital Discharge Survey and Nationwide Inpatient Sample data, and the National Health Interview Survey.

Main Outcome Measures—Pneumococcal disease cases prevented and incremental costs per quality-adjusted life year (QALY) gained.

Results—In the base case scenario, PCV13 given as a substitute for PPSV23 in current recommendations (i.e., vaccination at 65 years and at younger ages if comorbidities are present) cost $28,900/QALY gained compared with no vaccination and was more cost-effective than the currently recommended PPSV23 strategy. Routine PCV13 at ages 50 and 65 years cost $45,100/QALY compared with PCV13 substituted in current recommendations. Adding PPSV23 at age 75 to PCV13 at ages 50 and 65 years gained 0.00002 QALYs, costing $496,000/QALY gained. Results were robust in sensitivity analyses and alternative scenarios, except when low PCV13 effectiveness against nonbacteremic pneumococcal pneumonia was assumed or when greater childhood vaccination indirect effects were modeled. In these cases, PPSV23 as currently recommended was favored.

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Conclusions—Overall, PCV13 vaccination was favored compared to PPSV23, but the analysis is sensitive to assumptions about PCV13 effectiveness against NPP and the magnitude of potential indirect effects from childhood PCV13 on pneumococcal serotype distribution.

Introduction

The 23-valent pneumococcal polysaccharide vaccine (PPSV23) has been recommended for prevention of invasive pneumococcal disease (IPD) in adults since 1983[1]. Most studies show that PPSV23 provides some protection against IPD, but studies have reached contradictory conclusions for its prevention of nonbacteremic pneumococcal pneumonia (NPP)[1-2], which causes several hundred thousand illnesses annually in the US[3]. Large randomized controlled trials of PPSV23 conducted in developed countries have not found evidence of efficacy against NPP among community-dwelling older adults or among younger adults with chronic illness[1, 4-5]. Routine childhood vaccination with the 7-valent pneumococcal conjugate vaccine (PCV7) has dramatically decreased both IPD and NPP in children through both direct and indirect (herd immunity) vaccine effects[6-7] and reduced adult pneumococcal disease through indirect effects[6-9]. The introduction of a pediatric conjugate vaccine containing six additional serotypes (PCV13) is expected to further reduce pneumococcal disease in children and adults[10-11].

Prior analyses suggest that adult pneumococcal conjugate vaccination could prevent more disease than PPSV23, due to its potential effectiveness against both NPP and IPD[12]. Although PCV7 has been shown to prevent NPP in children[13], PCV13 effectiveness in preventing NPP in adults is currently unknown and the subject of an ongoing clinical trial[14]. In addition, routine childhood vaccination with PCV13 will likely result in further indirect effects in adults[10], perhaps limiting the potential benefits of adult vaccination. As PCV13 is currently under FDA licensure review for use among adults 50 years and older[15], decisions about vaccination policy must weigh tradeoffs between the possibility of decreased NPP vs. fewer serotypes covered by PCV13, on a background of childhood vaccination-related changes in pneumococcal epidemiology and suboptimal adult vaccination uptake[16]. To address these issues, we used decision modeling techniques to examine the effectiveness and cost-effectiveness of pneumococcal vaccination strategies among adult cohorts 50 years of age and older.

Methods

Using a Markov state-transition model (Figures 1 and 2), we examined six pneumococcal vaccination strategies developed by a Delphi expert panel process (see below): 1) no vaccination, 2) the present US Advisory Committee on Immunization Practices (ACIP) adult recommendations (vaccinate all persons with PPSV23 at age 65; those who received PPSV23 before age 65 for a comorbid condition are recommended to receive another dose at age 65 or later if at least 5 years have passed since the previous dose)[1], 3) substituting PCV13 for PPSV23 in current ACIP recommendations, 4) PCV13 at age 50 and PPSV23 at age 65, 5) PCV13 at ages 50 and 65, and 6) PCV13 at ages 50 and 65, then PPSV23 at age 75. Strategies were compared using identical hypothetical cohorts of 50 year old US adults, with cohorts followed as they aged. We used a lifetime time horizon, a societal perspective, and a 3% discount rate for costs and benefits, converting costs to 2006 US dollars[17]. Quality of life was modeled using health state utility weights, with 0 equaling death and 1 denoting perfect health; quality adjusted life years (QALY) are the product of the health state utility and the length of time in that state.

The Markov model followed cohorts yearly until death. Pneumococcal disease was assumed to occur as in the Box, where the risk of infection is modified the likelihood and

effectiveness of vaccination and by projected herd immunity effects from childhood PCV13. In the model, these factors varied by age and presence or absence of comorbidity. In the base case scenario, PPSV23 was assumed to have no effect on NPP[4], while PCV13 was assumed to protect against NPP; these assumptions were modified in sensitivity analyses. Individuals could be in health states where pneumococcal disease risk was average or high and, within high-risk health states, persons with immunocompromising conditions were considered separately from those with other comorbid conditions. Persons at average risk could transition to the high-risk group due to development of a comorbid condition. We assumed no transitions from high risk to average risk. Patients could become disabled or die from pneumococcal infection, or recover.

We used 2006 National Health Interview Survey (NHIS) data to segment cohorts into comorbid illness groups to model differential vaccine effectiveness and pneumococcal disease rates based on age and comorbidity, using Centers for Disease Control and Prevention (CDC) definitions for immunocompromising and other comorbid conditions[18]. Asthma and cigarette smoking were recently added as pneumococcal vaccination indications[1]. In the model, asthma was included as a comorbid condition; smoking was not, due to difficulties in capturing reliable smoking information in CDC data. We also used Framingham Study[19-22] and SEER[23] data to model age-related risk of comorbid conditions in the oldest age groups. Patients with both immunocompromising and other comorbid conditions were included in the immunocompromised group; persons with HIV were also assumed to be included in the immunocompromised group. Transitions from other comorbid conditions to immunocompromised were based on SEER age-specific cancer incidence rates[23].

CDC Active Bacterial Core surveillance (ABCs) data from 2007-2008 were used to model IPD rates and age-specific likelihood of illness from vaccine-contained serotypes (Table 1). We used previously published methods[12] to derive hypothetical "no vaccine" IPD rates. Deaths were modeled using US mortality tables[24]. For hospitalized NPP rates, we extrapolated from all-cause pneumonia hospitalization rates (Table 2), estimating that pneumococcal pneumonia accounts for 30% of all-cause pneumonia hospitalizations[3, 12, 25]. We used National Hospital Discharge Survey data[26] for our base case analysis, with Nationwide Inpatient Sample data[6] used in sensitivity analyses. We assumed that the relative likelihood of hospitalized NPP among age- and comorbidity-specific groups was similar to that observed for IPD, and used rate ratios to model this assumption. Age- and comorbidity-specific rate ratios for IPD, from ABCs data, were applied to NPP rates to calculate age- and comorbidity-specific hospitalized NPP rates (Table 3). We also assumed that the serotype distributions were similar for hospitalized NPP and IPD. Due to uncertainty regarding the age- and comorbidity-specific frequency and serotype distribution of outpatient NPP and its lower cost[27-28], we limited our analysis to hospitalized NPP.

As described previously[29], an expert panel, using the modified Delphi technique[30], estimated PPSV23 effectiveness against IPD (Table 4). A second Delphi panel, comprised of ACIP Pneumococcal Vaccines Working Group members, estimated PCV13 effectiveness against vaccine serotypes causing IPD and NPP (Table 5) and selected the vaccination strategies to be modeled. PCV13 relative effectiveness against NPP was estimated to be 18% lower than for IPD (range 10-60%) in healthy 50 year olds, 25% lower (range 10-60%) in healthy 65 year olds, and 30% lower (10-60%) in persons with immunocompromising and/or other comorbid conditions; these calculations' results are shown in Table 6. Disability after IPD was modeled using meningitis as a proxy, understanding that not all meningitis is disabling but other IPD syndromes can be. For disability after NPP[31], we used 50% of the IPD value and varied it from 0-100% in sensitivity analyses. Vaccination adverse event data and quality of life utilities were literature-based[32-34]. Vaccine[35], administration[36],

and average adverse event costs ($0.03 per dose[34]) came from published sources. IPD and NPP hospitalization costs were obtained from 2006 Healthcare Cost and Utilization Project data[37].

Potential indirect effects from childhood PCV13 were modeled in two steps. First, changes in adult IPD rates were extrapolated from indirect effects seen post-PVC7[9]. We assumed that age-specific decreases in IPD would occur in commonly carried serotypes (3, 6A, 7F, and 19A) added to PCV13, as was observed for colonizing PCV7 serotypes[9], and increases would occur in non-PCV13 serotype IPD. No herd effects were assumed for serotypes 1 and 5, which are considered uncommon colonizers[11, 38]. Next, age-specific changes in vaccine serotype distributions were modeled, based on observed changes after PCV7 introduction[8], leading to a diminished relative likelihood of PCV13 serotype IPD in the first 1-5 years after PCV13 licensure. Longer-term effects were modeled based on observed age-related serotype distribution changes. Potential indirect PCV13 effects for NPP were modeled using point estimates for decreases observed after PCV7 introduction[6].

In the base case scenario, we assumed 60.1% adherence to age-based vaccination recommendations and 33.9% adherence to comorbidity-based vaccination recommendations, based on observed PPSV23 uptake[16, 39]. In strategies modeling current vaccination recommendations, all persons with a comorbid condition diagnosed before age 50 were vaccinated at age 50. Persons aged 50 to 64 developing a comorbid condition were vaccinated that year, then revaccinated either at age 65 or five years after the first vaccination, whichever came last.

Table 7 depicts model parameter values. Parameters were varied individually in 1-way sensitivity analyses and varied simultaneously in probabilistic sensitivity analyses, where random draws from distributions were performed and the effectiveness or cost-effectiveness of each strategy calculated 3000 times. Distributions were chosen based on parameter characteristics and level of certainty. Parameters whose distributions were least certain (e.g., utility weights) were assigned uniform distributions, vaccine effectiveness estimates were assigned triangular distributions, and parameters whose distributions were most certain (i.e., derived from clinical trial or epidemiologic data) were assigned distributions based on data characteristics and ability to account for distribution skewness. In separate analyses, we varied the relative likelihood of IPD or NPP due to vaccine serotypes from 90-110% of the baseline values and considered greater herd immunity effects.

Results

Pneumococcal disease epidemiology

With no vaccination, the lifetime risk from age 50 onward for hospitalized NPP was 9.3%, for IPD was 0.86%, and for death due to pneumococcal disease was 1.8%. Thus, among the cohort of approximately 4.3 million US 50-year-olds in 2006[40], the model estimated 396,087 NPP hospitalizations, 36,576 IPD cases and 75,647 deaths due to pneumococcal disease over their lifetime. Table 8, top, summarizes the public health impact of different vaccination strategies. PPSV23 strategies prevented more IPD than strategies using only PCV13, while strategies using 2 scheduled PCV13 doses prevented more NPP.

In sensitivity analyses, results were most sensitive to variation in vaccine effectiveness estimates and magnitude of herd effects from childhood PCV13 vaccination on adult NPP. Using Nationwide Inpatient Sample data for all-cause pneumonia rates instead of the National Hospital Discharge Survey minimally affected results.

Due to the unknown effectiveness of adult PCV13 against NPP, we also performed a worst-case NPP scenario (Table 8, bottom), where PCV13 effectiveness against NPP was set at the low range of estimates (Table 6) and base case IPD effectiveness estimates for both vaccines were used. Despite worst-case assumptions, more total pneumococcal disease cases and deaths were prevented by strategies containing PCV13 compared to the current PPSV23 recommendation strategy.

Cost-effectiveness analysis

Incremental cost-effectiveness analysis results under base case assumptions are shown in Table 9 (top). In accordance with guidelines[17], we present results as incremental cost-effectiveness ratios, ordering strategies by cost and eliminating strategies that are strictly dominated (more costly and less effective) or extended dominated (having higher incremental cost-effectiveness ratios than more effective strategies)[41].

With no vaccination, the total per person cost of IPD and hospitalized NPP from age 50 onward was $1047. Compared to no vaccination, current PPSV23 recommendations (vaccination at age 65 and at younger ages if comorbidities are present) cost $34,600/QALY gained. However, this strategy is eliminated due to extended dominance, since its cost-effectiveness ratio is greater than that of the more effective PCV13 substituted in current recommendations strategy, which cost $28,900/QALY gained. PCV13 given routinely at ages 50 and 65 years cost $45,100/QALY compared with PCV13 substituted in current recommendations. PCV13 at ages 50 and 65 followed by PPSV23 at age 75 gained 0.00002 more QALYs per person and cost $496,000/QALY gained. There are no absolute criteria for cost-effectiveness but, in general, interventions costing <$20,000/QALY gained are felt to have strong evidence for adoption, interventions costing $20,000-$100,000/QALY have moderate evidence, and those costing >$100,000/QALY have weaker evidence for adoption[42-43].

When PCV13 effectiveness against NPP is set at low range estimates (Table 9, bottom), current PPSV23 recommendations were favored, costing $34,600/QALY gained. PCV13 substituted in current recommendations cost $131,000/QALY gained; other strategies had prohibitive cost-effectiveness ratios. If, in this scenario, PPSV23 effectiveness against IPD is also at the low estimates, the current PPSV23 recommendation strategy cost $60,200/QALY and PCV13 substituted in current recommendations cost $93,000/QALY gained.

The analysis was also sensitive to vaccine costs. PCV13 substituted into current recommendations cost >$100,000/QALY when PCV13 vaccination cost was >$237 (base case estimate=$128). The analysis was not sensitive to individual variation of other parameter values (Table 10).

A probabilistic sensitivity analysis of base case results is shown as a cost-effectiveness acceptability curve (Figure 3), showing the proportion of cost-effectiveness calculations that would be considered acceptable from a societal standpoint for various willingness-to-pay thresholds. This analysis, which includes the likelihood of worst-case scenario for effectiveness against NPP, PCV13 given routinely at ages 50 and 65 would be favored if willingness-to-pay (or acceptability) thresholds were >$50,000/QALY. Changing vaccine effectiveness distributions from triangular to uniform or beta distributions left results essentially unchanged.

In a series of separate sensitivity analyses on the base case model, we relaxed modeling assumptions to test model robustness. If PCV13 had no direct effects on adult nonbacteremic pneumonia, the current PPSV23 policy cost $34,600/QALY and all PCV13 strategies were strictly dominated (i.e., more costly and less effective). If greater herd

immunity effects on pneumococcal disease rates (leading to fewer IPD and NPP cases) were modeled, current recommendations using PCV13 cost $38,400/QALY and PCV13 at ages 50 and 65 cost $51,000/QALY gained. Modeling greater decreases in disease likelihood from a vaccine serotype (declining with age from a 16% relative likelihood of disease from PCV13 serotypes compared to nonvaccine serotypes at age 50, rather than from 24% in the base case) led to the current recommendations using PCV13 strategy being dominated, current recommendations using PPSV23 costing $38,900/QALY gained, and PCV13 at ages 50 and 65 costing $106,000/QALY. In the base case analysis, we assumed that 30% of hospitalized all-cause pneumonia was NPP. If NPP accounted for 20% pneumonia hospitalizations, current PPSV23 recommendations cost $34,400/QALY, PCV13 in current recommendations cost $59,100/QALY, and PCV13 at ages 50 and 65 cost $74,200/QALY.

We also examined scenarios where PPSV23 was effective against NPP. PCV13 at 50 and 65 would continue to be favored (at a $100,000/QALY criterion) if PPSV23 effectiveness against NPP was <44% at age 50 and <38% at age 65. At higher effectiveness levels, the currently recommended PPSV23 strategy was favored.

Discussion

Our analysis favors vaccinating adults with PCV13 instead of PPSV23, and suggests that PCV13 given either as a substitute for PPSV23 in current recommendations or routinely at ages 50 and 65 might reduce pneumococcal disease burden in an economically reasonable fashion. A two-dose PCV13 strategy at 50 and 65, although having a higher cost-effectiveness ratio, addresses the complexity of risk-based recommendations and is consistent with moves away from comorbidity-based strategies, exemplified by recent changes in influenza vaccination recommendations[44].

However, results favoring PCV13 were sensitive to assumptions regarding PCV13 effectiveness against NPP. If effectiveness against NPP is low, then current PPSV23 recommendations are favored, but if, in addition, PPSV23 effectiveness against IPD is at the experts' low range estimate, PCV13 substituted into current recommendations again becomes economically reasonable. This analysis highlights the tradeoffs that policy makers must consider when choosing among adult pneumococcal vaccination strategies. PPSV23 covers 23 serotypes and could prevent more IPD than PCV13 but, based on US and Western European studies, has no consistent effect on NPP[4-5]. Based on the experience with PCV7 program[6-7], PCV13 is likely to prevent NPP. Since NPP is much more common than IPD, PCV13, despite its narrower serotype coverage, should prevent more pneumococcal disease than PPSV23. However, when modeling the possibility of PPSV23 preventing NPP, PPSV23 could be favored, but only if its effectiveness against NPP is higher than would be expected based on trial results[4-5]. At present, PCV13 effectiveness against pneumonia in adults is unknown. However, PCV7 was consistently effective against pediatric pneumonia in randomized clinical trials[13, 46-48].

Results were also sensitive to the magnitude of indirect effects from childhood PCV13. Herd immunity from the added 6 serotypes will likely reduce disease rates in adults. Indirect effects of childhood PCV7 on carriage and IPD rates among adults have been documented[8-9, 49]. Decreases in all-cause pneumonia hospitalizations in adults 50 years and older were observed following PCV7 introduction, although these reductions were not statistically significant in one study[6], but were significant in another[7]. However, given documented decreases in IPD rates due to indirect effects, we modeled decreases in adult NPP rates based on published point estimates, which could bias the analysis against PCV13. In any case, larger than expected indirect effects from childhood PCV13 would reduce the value of adult PCV13 strategies.

Several limitations should be considered in interpreting our findings. The analysis is limited by the lack of data on PCV13 effectiveness. A randomized trial of PCV13 among 85,000 adults 65 years of age is currently underway in the Netherlands; data collection will end 12/2011 but results will not be available until 2013[14]. The magnitude of herd effects and changes in serotype distribution resulting from childhood PCV13 are also unknown. We modeled these based on data from the PCV7 experience. We excluded outpatient pneumonia due to difficulties in accurate estimation of disease rates and characteristics, and the relatively minor role of outpatient costs; again possibly biasing against PCV13. Other studies estimated that outpatient NPP accounted for 5% of adult pneumococcal disease costs[28, 50]. Our model is based on 50-year-old cohorts followed over their lifetime; this analysis does not consider cohorts of differing ages or other issues germane to ensuring population immunity, such as catch up vaccination. Finally, as infrastructure and resources to support adult vaccination are limited, achieving sufficient coverage with PCV13 is uncertain[39, 51].

In conclusion, our analysis suggests that PCV13 might prevent more pneumococcal disease compared to the current PPSV23 vaccination recommendations, while remaining economically reasonable. However, these conclusions are sensitive to assumptions regarding PCV13 effectiveness against NPP, PPSV23 effectiveness against IPD and NPP, and herd immunity effects. Model estimates of adult PCV13 impact would be strengthened by evidence of PCV13 effectiveness against NPP from ongoing clinical trials and availability of data on the indirect effects of childhood PCV13 on adult pneumococcal disease rates.

Acknowledgments

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Box.

Baseline probability of infection (pre-childhood PCV13) × Projected relative likelihood of infection (indirect effect, post- vs. pre-PCV13) × Relative likelihood of infection from a vaccine serotype (pre-PCV13) × Projected change in infection serotype likelihood (indirect effect) × Probability of being vaccinated × Probability of vaccine effectiveness
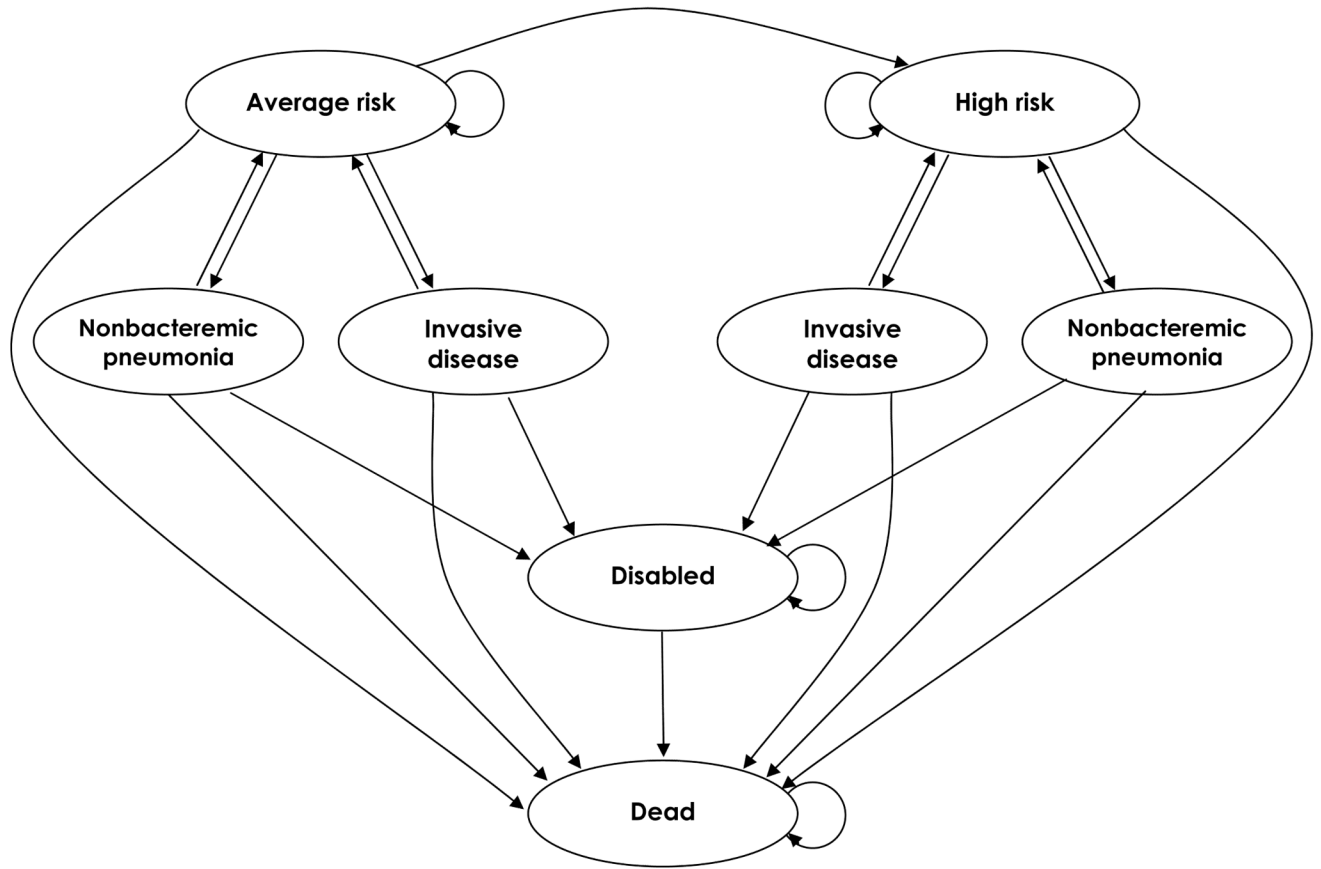
Figure 1. Schematic depiction of the Markov model for pneumococcal vaccination and infection
Model health states are shown as ovals. During yearly model cycles, transitions between
health states or remaining in the same health state can occur, represented by the arrows.
Transitions to pneumococcal disease states are based on vaccination effects and herd
immunity projections.
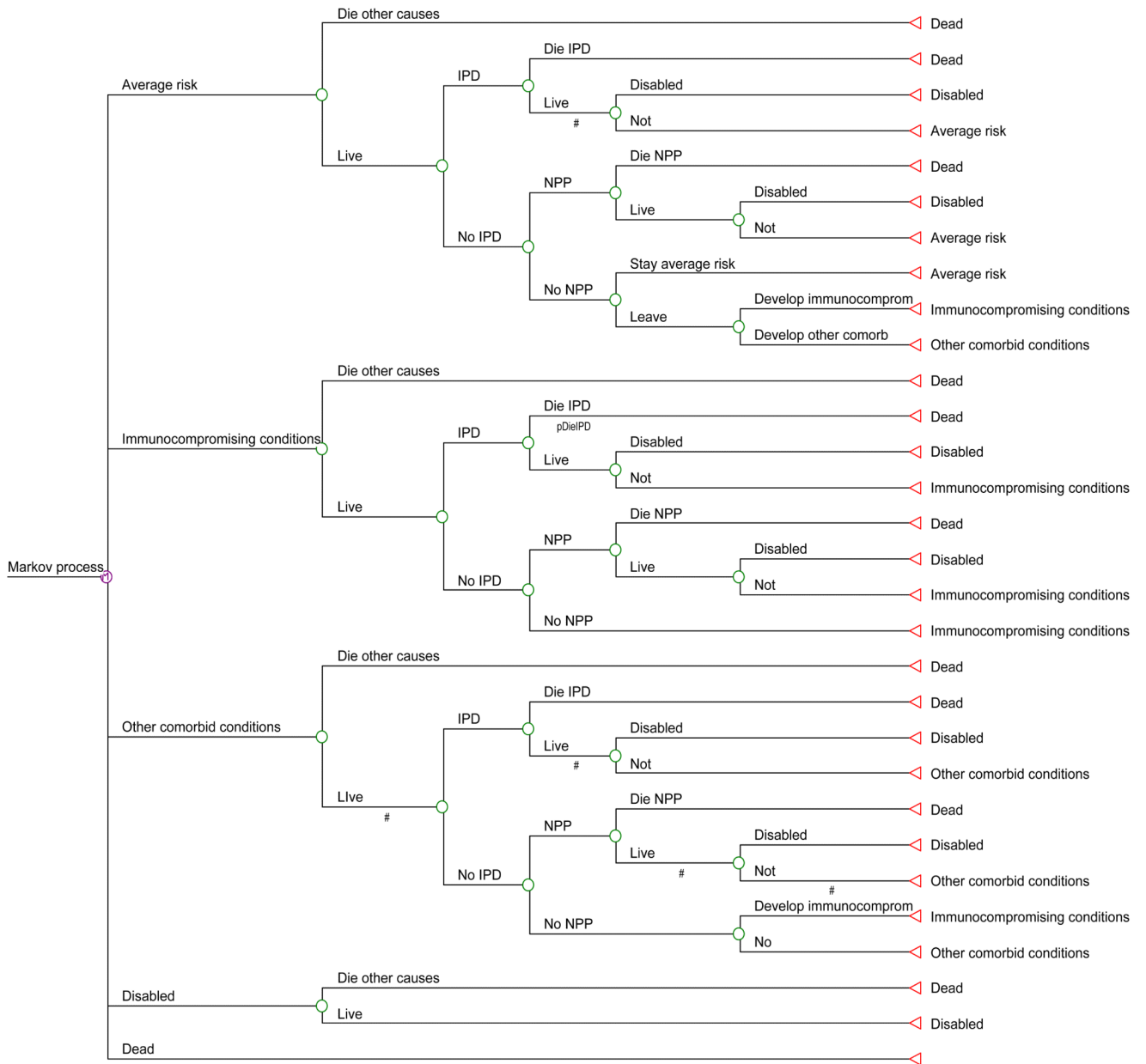
Figure 2. Markov cycle tree

The cycle tree gives more detail on the programming of the Markov model. Health states are the first branches off the Markov node. Pneumococcal diseases (invasive pneumococcal disease, IPD and nonbacteremic pneumococcal pneumonia, NPP) are modeled as virtual states ("tolls") within the tree structure. The triangular terminal nodes (on the left) depict the health states where portions of the cohort following that path will begin the next yearly cycle of the model.
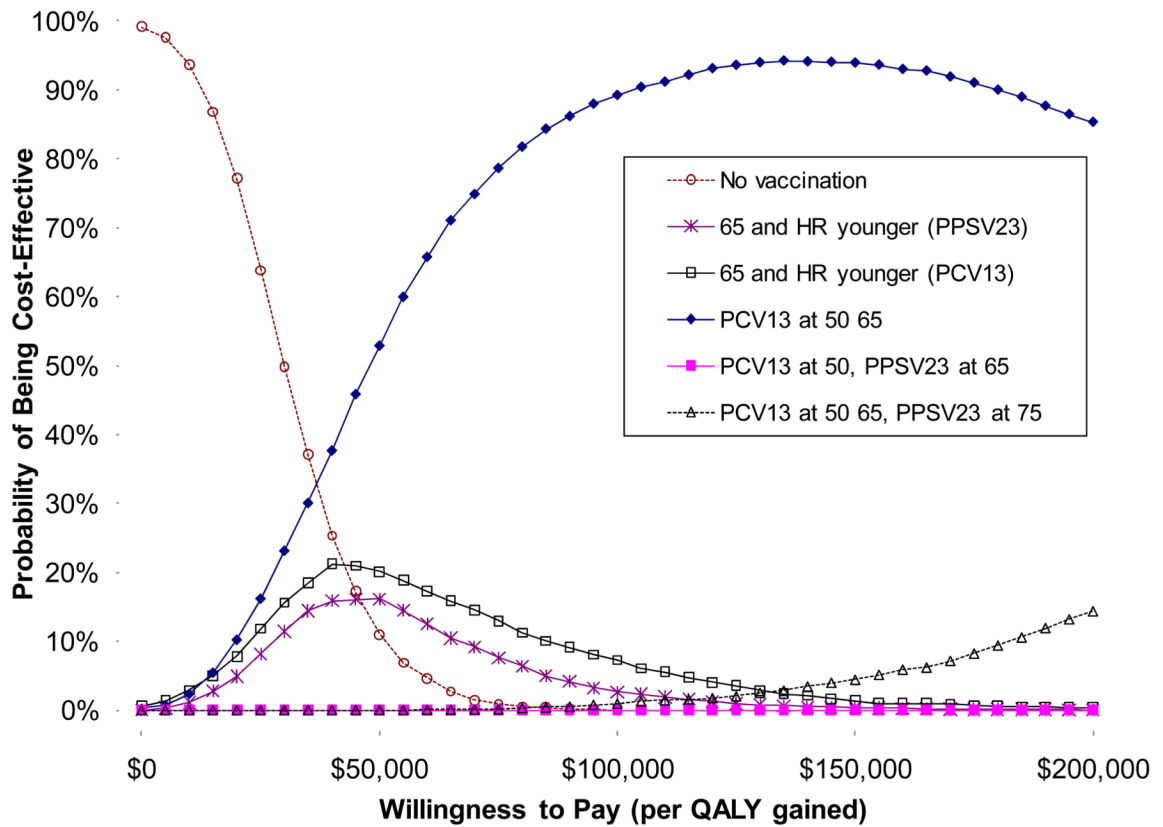
Figure 3. Probabilistic sensitivity analysis for adult pneumococcal vaccination strategies
Results are shown as a cost-effectiveness acceptability curve. The y-axis shows the
likelihood that strategies would be considered cost-effective for a given cost-effectiveness
willingness to pay (or acceptability) threshold.
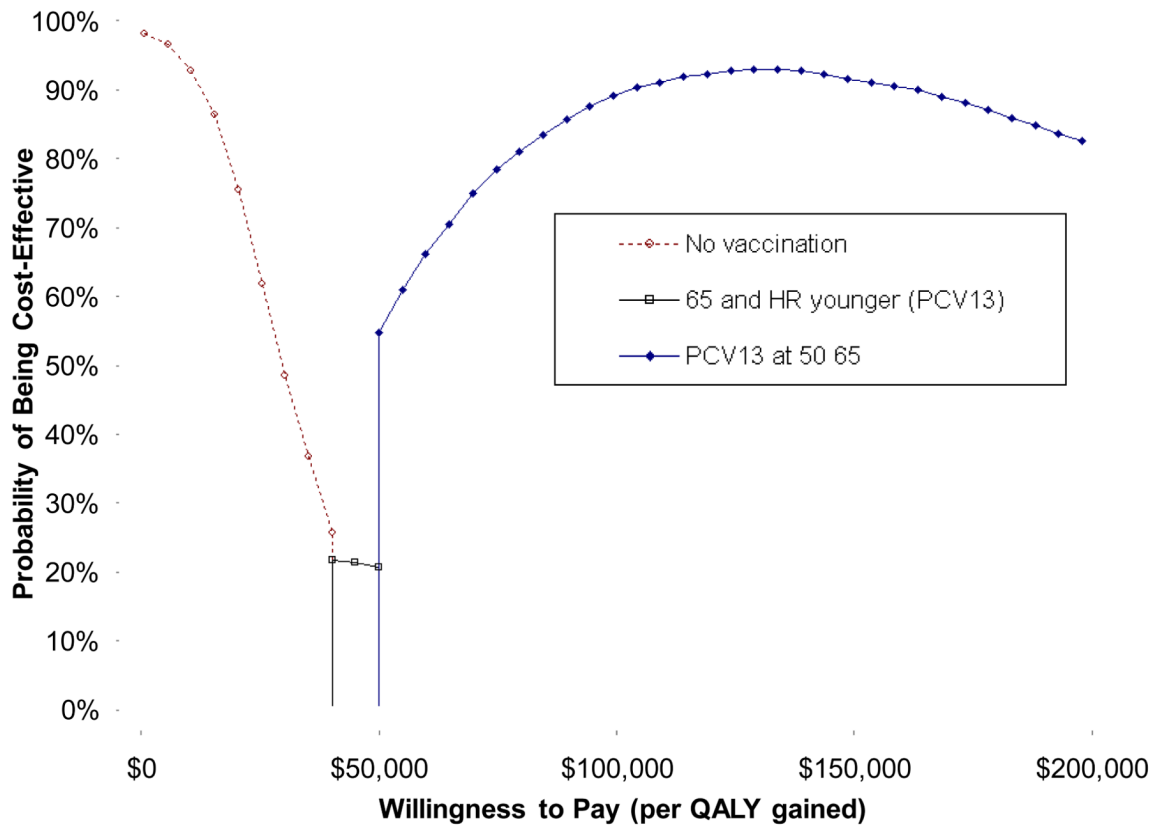
Figure 4. Cost-effectiveness acceptability frontier
The cost-effectiveness acceptability frontier depicts the strategy with the highest expected net benefit for a given willingness to pay threshold. The no vaccination strategy has the highest expected net benefit at values of $35,000/QALY, PCV13 substituted for PPSV23 in current recommendations is favored from $40,000-50,000/QALY, and PCV13 at ages 50 and 65 is favored at higher willingness to pay thresholds >$50,000/QALY.

Table 1

Characteristics of Invasive Pneumococcal Infections Based on the Active Bacterial Core Surveillance System[*]

	Ages 50-59	Age 60-69	Age 70-79	Age 80
Invasive pneumococcal disease rates (per 100,000 population per year)				
Total	19.6	25.9	33.9	60.1
No comorbid or immunocompromising conditions	9.2	13.1	16.2	33.9
1 immunocompromising conditions	67.1	58.5	54.1	64.3
1 comorbid conditions	39.2	39.2	48.5	97.2
PPSV23 vaccine serotype coverage (%)	73.3%	74.1%	65.8%	62.9%
PCV13 vaccine serotype coverage (%)	48.3%	48.7%	40.8%	40.8%
Disease outcome rates (per 100,000 population per year)				
Meningitis	1.4	1.6	1.3	1.3
Mortality	2.1	2.9	3.9	11.9

[*] Source: Active Bacterial Core Surveillance (ABCs) 2007-2008, Centers for Disease Control and Prevention, from all counties in ABCs PPSV23 = pneumococcal polysaccharide vaccine, PCV13 = 13-valent pneumococcal conjugate vaccine

Table 2

Annual US all-cause pneumonia hospitalization rates (per 100,000)

	Ages 45-64	Age 65+
National Hospital Discharge Survey[26]	334	1890
	Ages 40-64	Age 65+
Nationwide Inpatient Sample estimated[6]	328.1	2162.7

Table 3

Derived rates for hospitalized nonbacteremic pneumococcal pneumonia rates (per 100,000)

	Total	No conditions	Immunocompromised	Other comorbidities
Ages 45-64	100.2	47.3	343.6	201
Ages 65+	567	284.9	868	874.9

Table 4

Expert Panel Estimates of PPSV23 Effectiveness (%) in Preventing Vaccine Serotype Invasive Pneumococcal Disease

Vaccinee age/health:	Healthy 50 year olds*			Healthy 65 year olds*			Healthy 80 year olds*			Immunocompromised (all ages)*		
	Base case	Range		Base case	Range		Base case	Range		Base case	Range	
		Low	High		Low	High		Low	High		Low	High
Years post vaccination												
1	93	80	95	80	60	90	67	20	85	0	0	25.5
3	89	74	94.5	73	50	83	53	0	83.5	0	0	18
5	85	66	90	58	30.5	80	32	0	75	0	0	5
7	60	40	75	33	13	48	10	0	30	0	0	5
10	20	0	30	0	0	10	0	0	10	0	0	2.5
15	0	0	20	0	0	10	0	0	10	0	0	2.5

Base case denotes values used in the primary analysis. Values were varied over the ranges shown in sensitivity analyses.

*
Patients with other comorbid conditions vaccinated at these ages had the same base case and high range values, low range was decreased 25% relative to listed values

Table 5

Expert Panel Estimates of PCV13 Effectiveness (%) in Preventing Vaccine Serotype Invasive Pneumococcal Disease

Vaccinee age/health:	Healthy 50 year olds[*]			Healthy 65 year olds[*]			Immunocompromised (all ages)		
	Base case	Range		Base case	Range		Base case	Range	
		Low	High		Low	High		Low	High
Years post vaccination									
1	90	70	100	85	60	95	50	0	80
3	80	55	95	80	45	90	45	0	60
5	70	50	90	70	30	87	35	0	50
10	50	40	80	50	15	68	25	0	40
15	45	0	60	33	0	60	5	0	35

[*] Patients with other comorbid conditions vaccinated at these ages had base case estimates decreased 15% relative to listed values.

Table 6

Expert Panel Estimates of PCV13 Effectiveness (%) in Preventing Vaccine-Serotype Nonbacteremic Pneumococcal Pneumonia

Vaccinee age/health:	Healthy 50 year olds[*]			Healthy 65 year olds[*]			Immunocompromised (all ages)		
	Base case	Range		Base case	Range		Base case	Range	
		Low	High		Low	High		Low	High
Years post vaccination									
1	74	28	90	64	24	86	35	0	72
3	66	22	86	60	18	81	32	0	54
5	57	20	81	53	12	78	25	0	45
10	41	16	72	38	6	61	18	0	36
15	37	0	54	25	0	54	4	0	32

[*] Patients with other comorbid conditions vaccinated at these ages had base case estimates decreased 30% relative to listed values.

Table 7
Parameter Values and Ranges Examined in Sensitivity Analyses

Description	Base case	Range Low	High	Distribution	Source
Vaccine effectiveness (Delphi estimates by age/time)					
PPSV23 against IPD	Base	Low range	High range	Triangular	Expert panel (Table 4)
PCV13 against IPD	Base	Low range	High range	Triangular	Expert panel (Table 5)
PCV13 effectiveness against NPP relative to IPD effectiveness					Expert panel
Age 50	82% of base	40%	90%	Beta	
Age 65	75% of base	40%	90%	Beta	
Immunocompromised	70% of base	40%	90%	Beta	
Other comorbid conditions	70% of base	40%	90%	Beta	
PPSV23 effectiveness against NPP	0%	0%	80%	NA	
Relative risk of disease from vaccine serotypes	1	0.9	1.1	Uniform	Table 1
Vaccine adverse events					
Duration of symptoms (days)	3	1	8	Exponential	[32]
Probability per vaccinee after first vaccination	3.2%	2.2%	4.6%	Beta	[32]
Relative risk after subsequent vaccinations	3.3	2.1	5.1	Log normal	[32]
Disability					
Excess mortality per year	0.1	0	1	Uniform	Estimated
Risk relative to base case risk	1	0.5	1.5	Uniform	Table 1 [*]
Risk in nonbacteremic pneumonia relative to IPD	0.5	0	1	Uniform	Estimated
Case-fatality odds ratio for patients with immunocompromising or other comorbid conditions	1.5	1.3	1.8	Log normal	[8]
Utility weights					
Average risk population				Uniform	[34]
50-55 y	0.83	0.78	0.88		
55-60 y	0.81	0.76	0.86		
60-65 y	0.77	0.72	0.82		
65-70 y	0.76	0.71	0.81		
70-75 y	0.74	0.69	0.79		
75-80 y	0.70	0.65	0.75		
80-85 y	0.63	0.58	0.68		
>85 y	0.51	0.46	0.56		
High risk population				Uniform	[34]
50-55 y	0.72	0.67	0.77		
55-60 y	0.69	0.64	0.74		
60-65 y	0.63	0.58	0.68		
65-70 y	0.57	0.52	0.62		
70-75 y	0.54	0.49	0.59		
75-80 y	0.52	0.47	0.57		
80-85 y	0.51	0.46	0.56		

Description	Base case	Range Low	Range High	Distribution	Source
> 85 y	0.51	0.46	0.56		
Invasive pneumococcal disease	0.2	0.1	0.5	Uniform	[34]
Hospitalized nonbacteremic pneumonia	0.2	0.1	0.5	Uniform	Estimate[34]
Disabled	0.4	0.2	0.6	Uniform	Estimate[33]
Vaccine adverse event	0.9	0.8	0.99	Uniform	Estimate[33]
Costs					
Vaccine and administration					
PPSV23	$43	$25	$67	Gamma	35-36
PCV13	$128	$73	$196	Gamma	35-36
Invasive pneumococcal disease					
Discharged alive					
50-64	$24,519	base	base		[37]
65-74	$20,416	base	base		[37]
>74	$17,166	base	base		[37]
Died					
50-64	$33,778	base	base		[37]
65-74	$29,263	base	base		[37]
>74	$20,750	base	base		[37]
Nonbacteremic pneumonia					
Discharged alive					
50-64	$19,396	base	base		[37]
65-74	$16,925	base	base		[37]
>74	$13,258	base	base		[37]
Died					
50-64	$35,408	base	base		[37]
65-74	$28,288	base	base		[37]
>74	$21,560	base	base		[37]

PPSV23 = pneumococcal polysaccharide vaccine, PCV= pneumococcal conjugate vaccine, IPD = invasive pneumococcal disease, NPP = nonbacteremic pneumococcal pneumonia

*Using meningitis rates as a proxy for disability incidence

Table 8

Public health impact of various adult pneumococcal vaccination strategies in Markov models. Lifetime incidence of pneumococcal disease in 50-year-old cohorts

Base case analysis

	Hospitalized nonbacteremic pneumococcal pneumonia			Invasive pneumococcal disease			Pneumococcal disease deaths		
	Incidence/10^5	RR	Cases prevented*	Incidence/10^5	RR	Cases prevented*	Incidence/10^5	RR	Deaths prevented*
No vaccination	9292	1.0	-	858	1.0	-	1775	1.0	-
65 and HR younger (PPSV23)	9292	1.0	0	815	0.95	1834	1769	0.997	255
PCV13 at 50, PPSV23 at 65	9229	0.99	2648	822	0.96	1522	1762	0.993	523
65 and HR younger (PCV13)	9122	0.98	7217	833	0.97	1082	1749	0.985	1111
PCV13 at 50 65	8988	0.97	12944	830	0.97	1207	1729	0.974	1947
PCV13 at 50 65, PPSV23 at 75	8988	0.97	12944	822	0.96	1537	1728	0.974	1998

Low PCV13 effectiveness against nonbacteremic pneumococcal pneumonia *

	Hospitalized nonbacteremic pneumococcal pneumonia			Invasive pneumococcal disease			Pneumococcal disease deaths		
	Incidence/10^5	RR	Cases prevented*	Incidence/10^5	RR	Cases prevented*	Incidence/10^5	RR	Deaths prevented*
No vaccination	9292	1.0	-	858	1.0	-	1775	1.0	-
65 and HR younger (PPSV23)	9292	1.0	0	815	0.95	1834	1769	0.997	255
PCV13 at 50, PPSV23 at 65	9271	1.00	862	822	0.96	1522	1768	0.996	301
65 and HR younger (PCV13)	9224	0.99	2867	833	0.97	1082	1761	0.993	559
PCV13 at 50 65	9210	0.99	3489	830	0.97	1207	1760	0.992	632
PCV13 at 50 65, PPSV23 at 75	9210	0.99	3489	822	0.96	1537	1759	0.991	683

RR = relative risk, HR = high risk, PPSV23 = 23-valent pneumococcal polysaccharide vaccine, PCV13 = 13-valent pneumococcal conjugate vaccine, NA = not applicable, not included in probabilistic sensitivity analysis

*
PCV effectiveness against nonbacteremic pneumonia set at the low range estimates of the Delphi expert panel

Table 9

Cost-effectiveness analysis results

	Cost	Incremental Cost	Effectiveness (QALY)	Incremental Effectiveness (QALY)	ICER ($/QALY)
Base case					
No vaccination	$1,047	-	12.58345	-	-
65 and HR younger (PPSV23)[*]	$1,059	$12	12.58380	0.00035	(Ext Dom)
65 and HR younger (PCV13)	$1,080	$33	12.58461	0.00116	$28,900
PCV13 at 50, PPSV23 at 65	$1,119	$39	12.58449	−0.00012	(Dominated)
PCV13 at 50 65	$1,123	$43	12.58555	0.00094	$45,100
PCV13 at 50 65, PPSV23 at 75	$1,131	$8	12.58557	0.00002	$496,000
Worst case [†]					
No vaccination	$1,047	-	12.58345	-	-
65 and HR younger (PPSV23)[*]	$1,059	$12	12.58380	0.00035	$34,616
65 and HR younger (PCV13)	$1,092	$34	12.58405	0.00027	$131,486
PCV13 at 50, PPSV23 at 65	$1,127	$35	12.58402	-0.00003	(Dominated)
PCV13 at 50 65	$1,150	$58	12.58428	0.00023	$255,285
PCV13 at 50 65, PPSV23 at 75	$1,158	$8	12.58430	0.00002	$496,538

PCV13 = 13-valent pneumococcal conjugate vaccination; PPSV = 23-valent pneumococcal polysaccharide vaccine; QALY = quality adjusted life year; ICER = incremental cost-effectiveness ratio; HR=high risk conditions

Ext Dom = extended dominance (other strategies have lower cost-effectiveness ratios than this strategy) Dominated = other strategies are less costly and more effective than this strategy. Based on recommendations, strategies that are dominated by either mechanism are eliminated from further consideration in a cost-effectiveness analysis.

[*] The currently recommended adult pneumococcal vaccination strategy

[†] Lowest PCV13 effectiveness estimates against nonbacteremic pneumococcal pneumonia

Table 10

One-way sensitivity analysis: parameters whose variation results in 5% changes in incremental cost effectiveness ratios

	Base case value	Range values	Incremental cost-effectiveness ratio (per QALY)	
			PCV13 at 65 and HR younger	PCV13 at 50 65
Base case	-	-	**$28,900**	**$45,100**
Vaccine effectiveness estimates	Tables 4 & 5	Low range	$46,400	$175,000
		High range	$5,300	$76,700
PCV13 relative effectiveness against NPP				
Age 50	82% of base	40%	$28,900	$60,800
		90%	$28,900	$40,100
Age 65	75% of base	40%	$43,600	$45,100
		90%	$25,100	$45,100
Other comorbid conditions	70% of base	40%	$45,200	$64,300
		90%	$23,100	$36,300
RR of infection from vaccine serotypes	1	0.9	$33,000	$50,300
		1.1	$25,600	$40,800
Disability risk in NPP relative to IPD	0.5	0	$34,000	$53,000
		1	$24,800	$38,900
Case-fatality OR with immunocompromise or other comorbid conditions	1.5	1.3	$30,600	$47,300
		1.8	$26,700	$42,300
Vaccine and administration costs				
PPSV23	$43	$25	$36,700	$45,100
		$67	$28,900	$45,100
PCV13	$128	$73	$6,930	$16,900
		$196	$65,100	$79,900

QALY = quality adjusted life-year, PCV13 = 13-valent pneumococcal conjugate vaccine, PPSV23 = 23-valent pneumococcal polysaccharide vaccine, NPP = noninvasive pneumococcal pneumonia, IPD = invasive pneumococcal disease, RR = relative risk