Modeling of Cost Effectiveness of Pneumococcal Conjugate Vaccination Strategies in U.S. Older Adults

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Background: The 13-valent pneumococcal conjugate vaccine (PCV13) is approved by the U.S. Food and Drug Administration for adults, but its role in older adults is unclear.

Purpose: To compare PCV13 strategies to currently recommended vaccination strategies in adults aged ≥65 years.

Methods: Using a Markov model, the cost effectiveness of PCV13 and the 23-valent pneumococcal polysaccharide vaccine (PPSV23), alone or in combination, was estimated, in adults aged either 65 years or 75 years. No prior vaccination, prior vaccination, and vaccine hyporesponsiveness scenarios were examined. Pneumococcal disease rates, indirect childhood PCV13 effects, and costs were estimated using CDC Active Bacterial Core surveillance data and U.S. national databases. An expert panel estimated vaccine-related protection. A societal perspective was taken and outcomes were discounted 3% per year.

Results: In those aged 65 years, single-dose PCV13 cost $11,300 per quality-adjusted life-year (QALY) gained compared to no vaccination; at ages 65 and 80 years, PCV13 cost $83,000/QALY. In those aged 75 years, single-dose PCV13 cost $62,800/QALY gained. PPSV23 cost more and was less effective than PCV13. Results were sensitive to varying vaccine effectiveness and indirect effect estimates. In hyporesponsiveness scenarios, cost-effectiveness ratios increased by 37%–78% for single-dose strategies and 29%–35% for multiple-dose strategies.

Conclusions: Single-dose PCV13 strategies are likely to be economically reasonable in older adults.
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Introduction

Adults aged ≥65 years are at increased risk for pneumococcal disease because of immunosenescence and the presence of chronic illnesses that increase pneumococcal disease risk. As a result, this age group accounts for much of the approximately 175,000 pneumonia hospitalizations, 50,000 cases of bacteremia, and 3000 – 6000 meningitis cases occurring due to pneumococci annually in the U.S.[1] Moreover, case–fatality rates for pneumococcal bacteremia in the elderly are 12%–20% based on current data, much higher than that seen in younger adults.[2–5]

Two adult vaccines to prevent pneumococcal disease are now approved in the U.S. Licensed since 1983, the 23-valent pneumococcal polysaccharide vaccine (PPSV23) is currently recommended for all adults aged ≥65 years.[4] PPSV23 safety and effectiveness against invasive pneumococcal disease (IPD) are well established. However, PPSV23 effectiveness against the more common nonbacteremic pneumococcal pneumonia (NPP) has not been established.[6,7] Recommendations for PPSV23 use are clearly delineated by the CDC Advisory Committee for Immunization Practices (ACIP).[4]

The second vaccine, the 13-valent pneumococcal conjugate vaccine (PCV13) was approved by the U.S. Food and Drug Administration (FDA) in December 2011 for use in those aged ≥50 years. However, the CDC has not made recommendations for PCV13 use in adults that do not have immunocompromising conditions, owing to a number of scientific and public health uncertainties. A major issue is whether PCV13 prevents NPP in adults; a clinical trial to answer this question is ongoing.[8] A recent change in the CDC protocol for making decisions about

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vaccine policy is the use of the GRADE (grading of recommendations, assessment, development and evaluation) evidence-based framework that explicitly accounts for effectiveness, safety, and cost-effectiveness issues.[9] The CDC has recently made recommendations for PCV13 use, in combination with PPV23, in adults with immunocompromising conditions,[10] but recommendations in adults without those conditions await GRADE-framework evaluation.

The two vaccines differ in number of serotypes covered; mechanism for immunogenicity (T-dependent PCV13 versus T-independent PPSV23); potential immunologic interference with subsequent doses; immunogenicity duration; cost; and degree of effectiveness, particularly against NPP. However, no direct effectiveness comparisons are available. Studies of serologic opsonophagocytic antibody response have been conducted, but no serologic correlate of immunity in adults has been established.[11] Further, PCV13 use in children, which began in 2010, is likely to increase and extend the herd immunity effects seen since childhood PCV7 use began in 2000,[12,13] potentially reducing the usefulness of adult pneumococcal vaccination, because of decreased adult illness from PCV13 serotypes. Finally, decisions must account for background PPSV23 use, which was 59.7% in 2010.[14]

As the CDC examines evidence to inform vaccination recommendations, questions have arisen regarding the relative benefit of the two vaccines.[15] To assist decision-making about pneumococcal vaccination strategies in older adults who may have been previously vaccinated with PPSV23, Markov decision analyses were performed, examining pneumococcal vaccination strategies using either or both vaccines in two cohorts: those aged 65 years and those aged 75 years.

Table 1. Pneumococcal vaccination strategies examined among cohorts of 65-year-olds and 75-year-olds

	Single-vaccine strategies		Both vaccines strategies	
# of vaccines	PPSV23 only	PCV13 only	PPSV23 first	PCV13 first
65-year-olds				
1	65	65		
2	65, 75	65, 75	PPSV23: 65 PCV13: 75	PCV13: 65 PPSV23: 75
	65, 80	65, 80	PPSV23: 65 PCV13: 80	PCV13: 65 PPSV23: 80
3	65, 75, 85	65, 75, 85	PPSV23: 65 PCV13: 75, 85	PCV13: 65 PPSV23: 75, 85
75-year-olds				
1	75	75		
2	75, 85	75, 85	PPSV23: 75 PCV13: 85	PCV13: 75 PPSV23: 85

Note: Values show age at which vaccine is given for relevant strategy.
PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine

Methods

Fifteen pneumococcal vaccination strategies were examined in a cohort of 65-year-olds, and seven strategies were examined in a cohort of 75-year-olds, including a no-vaccination strategy in each cohort (Table 1). A Markov state-transition model was used (Appendix A, available online at www.ajpmonline.org), following cohorts yearly over their lifetime. Cohorts were designed to be similar to the U.S. population, using 2006 National Health Interview Survey (NHIS) data to model incidence and prevalence of comorbid conditions, as described previously.[16]

Individuals began the model at average or high risk for pneumococcal disease, based on the likelihood of immunocompromising conditions or other comorbid conditions as defined by the CDC.[12] People in either risk group could become ill because of invasive pneumococcal disease or nonbacteremic pneumococcal pneumonia, with that risk modified by vaccination, the likelihood of vaccination, waning vaccine immunity over time, and the likelihood and magnitude of indirect (herd immunity) effects on illness rates and pneumococcal serotype distribution. With illness, patients could recover, become disabled, or die. Individuals could transition from average risk to high risk based on the likelihood of developing a comorbid condition, but could not go from high to average risk. In the high-risk group, individuals with immunocompromising conditions were considered separately from those with other comorbid conditions (not shown in Appendix A [online at www.ajpmonline.org]). Patients with both an immunocompromising condition and another comorbid condition were considered to be in the immunocompromised health state. Patients in all states could also die of other causes, based on U.S. mortality tables.[17]

The model used a lifetime time horizon, with costs and effectiveness considered from the societal perspective and discounted 3% per year.[18] The cost base year was 2006. The effectiveness term was quality-adjusted life-years, calculated by multiplying the quality-of-life utility value (where 0=death and 1=perfect health) of a health state by the time spent in that state summed over all states and over time.

The CDC Active Bacterial Core surveillance (ABCs) data from 2007–2008 (Table 2) were used to model the age- and comorbidity-specific IPD risk, using CDC methods to calculate theoretic IPD incidence if PPSV23 was not being used.[19] Case–fatality rates were

Table 2. Characteristics of invasive pneumococcal infections based on the active bacterial core surveillance system[a]

	Age (years)				
	65–69	70–74	75–79	80–84	≥85
Invasive pneumococcal disease rates (per 100,000 population per year)					
Total	25.9	33.9	33.9	60.1	60.1
No comorbid or immunocompromising conditions	13.1	16.2	16.2	33.9	33.9
≥1 comorbid conditions	39.2	48.5	48.5	97.2	97.2
≥1 immunocompromising conditions	58.5	54.1	54.1	64.3	64.3
Disease outcome rates (per 100,000 population per year)					
Meningitis	1.6	1.3	1.3	1.3	1.3
Mortality	2.9	3.9	3.9	11.9	11.9
PCV13 vaccine serotype coverage (%)	48.7	40.8	40.8	40.8	40.8
PPSV23 vaccine serotype coverage (%)	74.1	65.8	65.8	62.9	62.9

[a]Source: Active Bacterial Core Surveillance (ABCs) 2007–2008, CDC, from all counties in ABCs
PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine

obtained from ABCs data and other CDC sources.[12] Meningitis incidence was used as a proxy for the likelihood of IPD-related disability. IPD serotype distributions were also obtained from ABCs data.

An expert panel estimated PPSV23 effectiveness against IPD using the modified Delphi technique (Appendix B, available online at www.ajpmonline.org), while a second Delphi panel, composed of ACIP Pneumococcal Vaccines Working Group members, estimated PCV13 effectiveness against vaccine serotypes causing IPD and NPP (Appendixes C and D, available online at www.ajpmonline.org), as described previously.[15,16] PCV13 relative effectiveness against NPP as compared to IPD was estimated as 18% lower in healthy adults aged 50 years, 25% lower in healthy adults aged 65 years, and 30% lower in those with immunocompromising and/or other comorbid conditions. Linear interpolation from experts' age-specific estimates was used to estimate effectiveness in those vaccinated at age 75 or 85 years.

Nonbacteremic pneumococcal pneumonia rates were calculated assuming that 30% of all-cause pneumonia hospitalizations from the National Hospital Discharge Survey[20] were due to pneumococcus. In sensitivity analyses, the 30% assumption was varied and all-cause pneumonia rates from another data source, the Nationwide Inpatient Sample, were used.[21] For hospitalized NPP, it was assumed that pneumococcal serotype distribution was similar to that of IPD and that disability occurred at 50% of the frequency seen in IPD. Age- and comorbidity-specific hospitalized NPP rates were calculated as described previously,[15] assuming hospitalized NPP rate ratios were the same as the IPD rate ratios in that age and comorbidity group and applying IPD rate ratios from ABCs data to NPP rates to calculate age- and comorbidity-specific hospitalized NPP rates (Appendix E, available online at www.ajpmonline.org). Nonhospitalized NPP was not considered in the current model, given its lower costs and considerable uncertainty regarding frequency and serotype characteristics[22,23]; this modeling choice could bias against PCV13.[24]

Indirect effects from childhood PCV13 vaccination on adult disease were modeled in terms of both decreases in pneumococcal disease rates and changes in pneumococcal disease serotype distributions. Based on changes seen post PCV7, decreases in IPD rates from the carried serotypes added to PCV13 (3, 6A, 7F, and 19A); no decrease in IPD from the added noncarried serotypes (1 and 5); and increased IPD from nonvaccine serotypes (replacement disease) were modeled. Decreased NPP rates were modeled based on point-estimate decreases in observed all-cause hospitalized pneumonia rates post PCV7[21]; these decreases were not significant in adults aged ≥50 years, which could bias model results against PCV13 strategies. Changes in serotype distributions were, in the short term, based on observed changes after PCV7 introduction and, over the longer term, based on observed age-related serotype changes.

For base-case scenarios, no prior pneumococcal vaccination was assumed. In addition, scenarios where prior vaccination and vaccine hyporesponsiveness occurred were examined, as were scenarios where prior vaccination either had no effect on the immunogenicity of subsequent vaccinations or decreased the immune response of subsequent vaccination by a relative value of 20%. Given no clinical trial data regarding adult PCV13 effects on NPP, a worst-case scenario for PCV13 effectiveness against NPP, using low-range effectiveness estimates from the Delphi expert panel, was also analyzed.

All parameters listed in Table 3 were varied individually in one-way sensitivity analyses. Parameter values were examined in probabilistic sensitivity analyses, simultaneously varying them over distributions and calculating incremental cost-effectiveness ratios 3000 times via random draws from each distribution. Parameter characteristics and level of uncertainty governed the type of distribution used. Vaccine effectiveness estimates were assigned triangular distributions, and beta distributions used for effectiveness against NPP relative to IPD. Parameters with the greatest level of uncertainty, such as disability estimates and utility weights, were assigned uniform distributions; and those obtained from clinical or epidemiologic data were varied over distributions relevant to their data characteristics. Finally, scenarios varying herd immunity, vaccine effectiveness, and NPP frequency assumptions were examined, as was a scenario where PPSV23 effectiveness against NPP was assumed.

Table 3. Parameter values and ranges examined in sensitivity analyses

Description	Base case	Range		Distribution	Source
		Low	High		
Vaccine effectiveness (Delphi estimates by age/time)					
PPSV23 against IPD	Base	Low range	High range	Triangular	Expert panel
PCV13 against IPD	Base	Low range	High range	Triangular	Expert panel
PCV13 effectiveness against NPP relative to IPD effectiveness					
Aged ≥65 years	75% of base	40%	90%	Beta	Expert panel
Immunocompromised	70% of base	40%	90%	Beta	Expert panel
Other comorbid conditions	70% of base	40%	90%	Beta	Expert panel
PPSV23 effectiveness against NPP (%)	0	0	80	NA	Huss et al.[6] and Moberley et al.[7]
Relative risk of disease from vaccine serotypes	1	0.9	1.1	Uniform	Table 1
Vaccine adverse events					Jackson et al.[25]
Duration of symptoms (days)	3	1	8	Exponential	
Probability per vaccinee after first vaccination (%)	3.2	2.2	4.6	Beta	
Relative risk after subsequent vaccinations	3.3	2.1	5.1	Log normal	
Disability					
Excess mortality per year	0.1	0	1	Uniform	Estimated
Risk relative to base-case risk	1	0.5	1.5	Uniform	Table 2
Risk in nonbacteremic pneumonia relative to IPD	0.5	0	1	Uniform	Estimated
Case–fatality OR for patients with immunocompromising or other comorbid conditions	1.5	1.3	1.8	Log normal	Lexau et al.[12]
UTILITY WEIGHTS					
Average-risk population (age in years)				Uniform	Sisk et al.[26]
65–70	0.76	0.71	0.81		
71–75	0.74	0.69	0.79		
76–80	0.70	0.65	0.75		
81–85	0.63	0.58	0.68		
>85	0.51	0.46	0.56		
High-risk population (age in years)				Uniform	Sisk et al.[26]
65–70	0.57	0.52	0.62		
71–75	0.54	0.49	0.59		
76–80	0.52	0.47	0.57		
81–85	0.51	0.46	0.56		
>85	0.51	0.46	0.56		
Invasive pneumococcal disease	0.2	0.1	0.5	Uniform	Sisk et al.[26]
Hospitalized nonbacteremic pneumonia	0.2	0.1	0.5	Uniform	Estimate
Disabled	0.4	0.2	0.6	Uniform	Estimate
Vaccine adverse event	0.9	0.8	0.99	Uniform	Estimate

(continued on next page)

Table 3. *(continued)*

Description	Base case	Range		Distribution	Source
		Low	High		
COSTS ($)					
Vaccine and administration					Centers for Medicare & Medicaid Services[27] and CDC[28]
PPSV23	43	25	67	Gamma	
PCV13	128	73	196	Gamma	
Invasive pneumococcal disease					NIS
Discharged alive (age in years)					
65–74	20,416	Base	Base	NA	
>74	17,166	Base	Base	NA	
Died (age in years)					
65–74	29,263	Base	Base	NA	
>74	20,750	Base	Base	NA	
Noninvasive pneumonia					NIS
Discharged alive (age in years)					
65–74	16,925	Base	Base	NA	
>74	13,258	Base	Base	NA	
Died (age in years)					
65–74	28,288	Base	Base	NA	
>74	21,560	Base	Base	NA	

IPD, invasive pneumococcal disease; NA, not applicable; NIS, nationwide inpatient sample; NPP, nonbacteremic pneumococcal pneumonia; PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, pneumococcal polysaccharide vaccine

Results

Table 4 summarizes incremental cost-effectiveness ratios (ICERs) for non-dominated strategies. Dominated strategies are either more expensive and less effective than other strategies or have higher ICERs than more effective strategies[29]; in accordance with recommendations, dominated strategies are eliminated from further consideration.[18] In the base-case analysis (Table 4, top), PPSV23 strategies were more costly (when considering both vaccination and pneumococcal disease costs) and less effective than PCV13 strategies and thus were dominated by them in the base-case scenario and are not shown in Table 4.

A worst-case analysis, using the experts' low-range estimate for PCV13 effectiveness against NPP (Table 4, bottom), showed that PCV13 strategies were no longer preferred, but that PPSV23 strategies have relatively high ICERs, particularly in those aged 75 years. There is no U.S. cost-effectiveness criterion; however, ICERs <$20,000 per QALY gained are generally considered a "good buy," whereas those >$100,000 per QALY are often felt to be an expensive use of healthcare resources.[30,31] By these criteria, a single PPSV23 at age 65 years would be the only strategy considered economically reasonable for those aged either 65 years or 75 years when PCV13 effectiveness against NPP is assumed to be low.

Cases and deaths prevented by vaccination are summarized in Appendixes F and G (available online at www.ajpmonline.org). In the base-case analysis for those aged 65 years (Appendix F, available online at www.ajpmonline.org), 3.2% of NPP cases (or 7453 cases in the U.S. cohort of about 2.6 million adults aged 65 years[32] over their lifetime) could be prevented by a PCV13 given at age 65 years, with 1.0%–1.4% absolute risk decreases in NPP with subsequent PCV13 doses. More deaths are prevented with PCV13 strategies, paralleling NPP cases prevented.

In contrast, more IPD cases are prevented by PPSV23 strategies (3.7%–7.0%), but PCV13 strategies prevent more hospitalized pneumococcal cases (i.e., IPD plus hospitalized NPP), because of the lower likelihood of IPD compared to NPP. Similar results were seen in the base-case analysis for the cohort of

Table 4. Cost-effectiveness results for pneumococcal vaccination strategies among cohorts of 65- and 75-year-olds[a]

Cohort age (years)	Strategy	ICER (per QALY), $
Base case		
65	PCV13: 65	11,300
	PCV13: 65, 80	83,000
	PCV13: 65, 75	263,000
	PCV13: 65, 75, 85	272,000
75	PCV13: 75	62,800
	PCV13: 75, 85	278,000
Worst-case PCV13 effectiveness against nonbacteremic pneumonia		
65	PPSV23: 65	98,600
	PCV13: 65	132,000
	PCV13: 65; PPSV23: 80	173,000
	PCV13: 65; PPSV23: 75, 85	853,000
	PCV13: 65, 75, 85	2,640,000
75	PPSV23: 75	345,000
	PPSV23: 75, 85	392,000
	PCV13: 75; PPSV23: 85	776,000
	PCV13: 75, 85	1,690,000

Note: Values following vaccine names are ages, in years, at which vaccines are given.
[a]Non-dominated strategies
ICER, incremental cost-effectiveness ratio; PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, pneumococcal polysaccharide vaccine; QALY, quality-adjusted life-year

those aged 75 years.[32] When PCV13 effectiveness against NPP was at its lowest estimated levels (Appendix G, available online at www.ajpmonline.org), 68%–86% fewer pneumococcal disease deaths were prevented, highlighting the importance of NPP prevention as a driver of analysis results.

Under base-case assum>ptions, cost-effectiveness results were sensitive to variation of vaccine effectiveness estimates and PCV13 costs in one-way sensitivity analyses (Appendix H, available online at www.ajpmonline.org). In those aged 65 years, a single PCV13 remained economically reasonable when these parameters were varied, whereas PCV13 at ages 65 and 80 years cost more than $100,000 per QALY gained when vaccine effectiveness was low or PCV13 costs were high. Similar findings occurred when a cohort entering the model at age 75 years received PCV13 at age 75 years.

Probabilistic sensitivity analyses were performed (Figure 1), where parameter values were simultaneously varied over distributions 3000 times. In those aged 65 years, PCV13 at age 65 years was favored when willingness-to-pay (or acceptability) thresholds are $20,000–$80,000 per QALY gained, whereas PCV13 at 65 years and 80 years was favored at thresholds of $90,000/QALY or more. In those aged 75 years, PCV13 at age 75 years was favored for thresholds of $70,000/QALY or more.

These results were tempered by scenarios where prior vaccination and hyporesponsiveness (or tolerance) from prior vaccination are examined (Figure 2). When prior vaccination and 80% effectiveness of subsequent vaccinations was assumed, large increases in incremental cost-effectiveness ratios were seen for single-dose strategies: by 79% in those aged 65 years and by 37% in those aged 75 years. Two vaccinations administered to 65-year-olds in this scenario at 65 years and 80 years resulted in a 35% increase, to $112,000 per QALY gained.

Other scenario analyses were performed, examining assumptions regarding herd immunity effects, vaccine effectiveness against IPD and NPP, and the frequency of NPP as

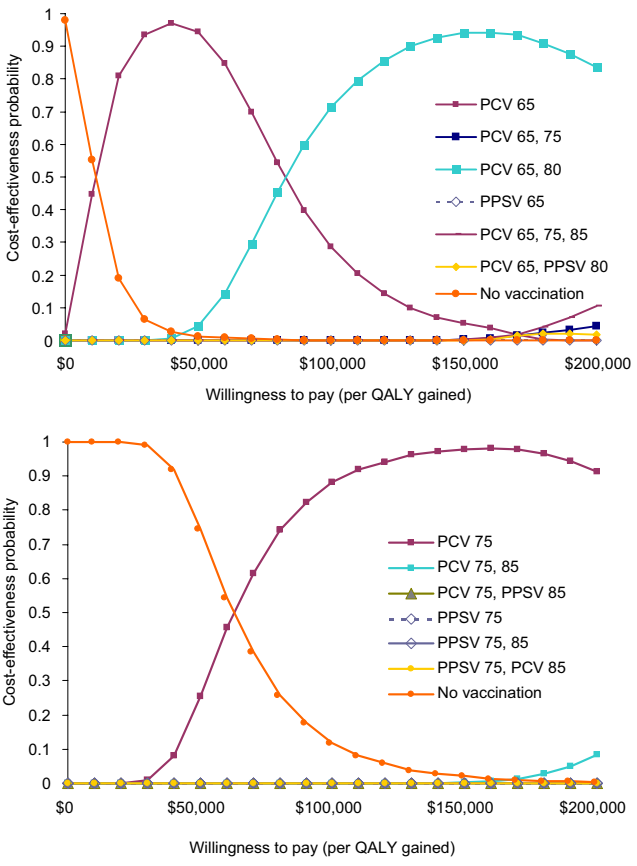

Figure 1. Probabilistic sensitivity analysis
Note: Results are depicted as cost-effectiveness acceptability curves. Cohorts of 65-year-olds (top) and 75-year-olds (bottom) show the probability that strategies would be considered cost effective for a range of cost-effectiveness willingness-to-pay (or acceptability) thresholds. Numbers following vaccine names indicate age (in years) at which they are given.
PCV, pneumococcal conjugate vaccine; PPSV, pneumococcal polysaccharide vaccine; QALY, quality-adjusted life-year

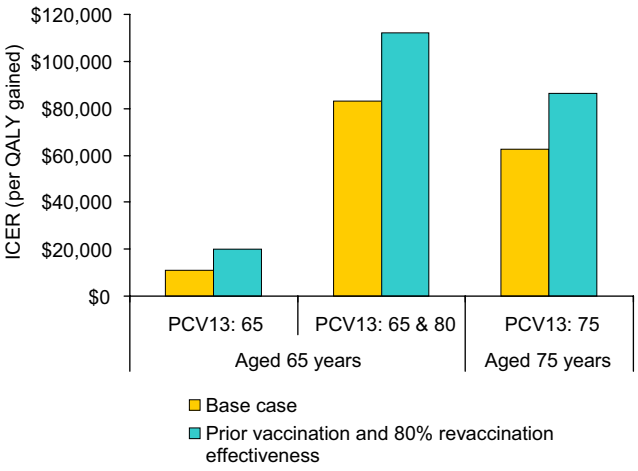

Figure 2. Sensitivity analysis, effect of prior vaccination and hyporesponsiveness

Note: The lighter bars depict base-case results for strategies costing <$100,000 per QALY gained. The base case assumed that no prior pneumococcal vaccination had occurred and that no hyporesponsiveness occurred in multiple-dose vaccination strategies. The darker bars depict results when prior vaccination is assumed and decreased immune response results from subsequent vaccinations. Numbers following vaccine names indicate age (in years) at which they are given.

ICER, incremental cost-effectiveness ratio; PCV13, 13-valent pneumococcal conjugate vaccine; QALY, quality-adjusted life-year

a cause of hospitalized pneumonia (Appendix I, available online at www.ajpmonline.org). In both age cohorts, larger herd immunity effects that lead to fewer pneumococcal disease cases did not affect the favorability of single-dose PCV13 strategies; however, greater herd immunity effects on serotype distributions left all vaccination strategies with unfavorable cost-effectiveness ratios. When no PCV13 direct effects on NPP were assumed, all PCV13-only strategies were dominated, and PPSV23 in 75-year-olds had an expensive cost-effectiveness ratio. If both vaccines have low effectiveness, vaccination strategies would not be favored for either age cohort when a $100,000 per QALY gained criterion is used. If NPP comprises 20% of all-cause pneumonia, rather than 30% as in our base case, the cost effectiveness of PCV13 at age 75 years increases to slightly more than $100,000/QALY. Results were not sensitive to variation of illness-related disability rates.

Finally, the assumption that PPSV23 is ineffective in preventing NPP was relaxed. In those aged 65 years, PPSV23 would need to be >71% effective against NPP for PPSV23 strategies to be preferred over PCV13 strategies when a $100,000 per QALY cost-effectiveness criterion is used. In those aged 75 years, PPSV23 would have to be >53% effective for it to be preferred.

Discussion

Under base-case assumptions, PCV13 strategies for patients aged 65–75 years were favorable from clinical and economic standpoints. Over the lifetime of the U.S. cohort of about 2.6 million 65-year-olds, 7453 NPP cases could be prevented by a PCV13 given at age 65 years, and 9827 cases by a two-dose strategy at ages 65 years and 80 years. The corresponding cost-effectiveness ratios were $11,300/QALY gained for a single dose and $83,000/QALY for the two-dose strategy. In the base-case analysis, PPSV23 strategies were more costly and less effective than PCV13 strategies, because of more disease and the greater costs of disease when PPSV23 was used.

At age 65 years, single-dose PCV13 strategy results changed less with differing assumptions. Assumptions that affected results were vaccine effectiveness, including PCV13 effectiveness against NPP, greater herd immunity leading to decreased disease from vaccine serotypes, increased vaccine price, and hyporesponsiveness after previous vaccine use. A single PPSV23 at age 65 years was the only strategy considered economically reasonable for those aged either 65 years or 75 years at low-range PCV13 effectiveness against NPP. Neither vaccine would be economically reasonable if both PCV13 and PPSV23 were relatively ineffective.

Herd immunity effects from childhood PCV7 on serotype carriage and IPD rates among adults have been documented.[12,13,33] Some increase in herd immunity for the six additional serotypes, due to childhood PCV13 use, will likely reduce pneumococcal disease rates in adults, although some of the new serotypes are not thought to be carried (e.g., Serotypes 1 and 5) and noncarriage might decrease vaccine herd effects on those serotypes. The current base case included projected changes in herd immunity, but the magnitude of those changes is uncertain, a potential limitation of the analysis. Greater herd immunity effects will make PCV13 less cost effective, because less disease will be caused by PCV13 serotypes.

The current analyses highlight tradeoffs that vaccine policymakers must consider when choosing among adult pneumococcal vaccination strategies: number of serotypes covered by each vaccine versus the much greater likelihood of NPP compared to IPD and the degree of protection against NPP afforded by vaccination. Although PPSV23 covers 23 serotypes and could potentially prevent more IPD than PCV13, there is no consistent effect on NPP among community-dwelling elderly adults according to meta-analyses of large RCTs.[6,7] At present, PCV13 effectiveness against pneumonia in adults is unknown. However, conjugate pneumococcal vaccines were consistently efficacious against pediatric pneumonia in RCTs.[10,34]

A randomized trial of PCV13 among 85,000 adults aged ≥65 years is currently underway in the Netherlands[8]; the study's final data collection date is August 2013[35] and it is not clear when results will become available. Based on the experience with pneumococcal conjugate vac-

cine,[10,34] PCV13 is likely to prevent NPP. Given that NPP is much more common than IPD, PCV13, despite its narrower serotype coverage, should prevent more pneumococcal disease than PPSV23.

Hyporesponsiveness, also called tolerance, is the decreased vaccination response occurring after previous vaccination, which has been documented in people receiving PCV7 after prior PPSV23 use.[36] However, in people receiving PPSV23, PCV7 was more immunogenic than repeat PPSV23.[37] At longer intervals—5 years or longer between PPSV23 doses—hyporesponsiveness may not be a major issue.[11,38] Multiple pneumococcal conjugate vaccine doses do not lead to hyporesponsiveness.[39] In hyporesponsiveness scenarios, large increases in incremental cost-effectiveness ratios were seen for single-dose strategies: 79% in 65-year-olds and 37% in 75-year-olds (Figure 2), similar to that seen in prior analyses examining repeat PPSV23 doses and the possibility of hyporesponsiveness.[40] The potential for hyporesponsiveness could affect results since the PPSV23 vaccination rate is about 60% among those aged ≥65 years; ensuring an interval of ≥4 years between vaccine doses may ameliorate much of this concern.[11,38]

Limitations of the current analyses include the lack of data on PCV13 effectiveness against NPP in adults. Outpatient NPP was not considered in the analysis because of difficulties in accurate estimation of its frequency and its relatively low costs, possibly biasing against PCV13 use. Other studies estimated that outpatient NPP accounts for ≤5%–7% of adult pneumococcal disease costs.[23,24,41] Other limitations include unknown timing of herd effects and unknown likelihood of replacement disease from nonvaccine serotypes.

Conclusion

The current analyses suggest that PCV13 should prevent more pneumococcal disease and be economically favorable when compared to the currently recommended PPSV23. Results favoring single-dose PCV13 strategies were relatively robust in sensitivity analyses but were sensitive to assumptions regarding PCV13 and PPSV23 effectiveness, herd immunity, and hyporesponsiveness when prior pneumococcal vaccination had occurred. Given these findings, policymakers can prudently await data on PCV13 effectiveness and herd immunity effects to inform PCV13 recommendations for older adults.

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Appendix

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.amepre.2012.11.035.