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Simplified Pneumococcal Vaccination Schedules for Adults Age 50 and

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Abstract

Background: In 2014 the Advisory Committee on Immunization Practices (ACIP) approved a dose of 13-valent pneumococcal conjugate vaccine (PCV13) for all adults at age 65 years. This further complicated the pneumococcal vaccination schedule, which was already one of the most complicated schedules.

Objective: This study documents simplified schedules that were considered and discarded by the pneumococcal working group before making the most recent recommendation. We examined the marginal cost-effectiveness of several simplified schedules for older adults (age 50+ years) when compared with current recommendations. Our primary outcome was the cost-effectiveness ratio of quality-adjusted life years to cost.

Methods: We used a probabilistic model following a cohort of 50 year-olds with separate vaccination coverage and disease incidence data for healthy adults and adults at increased risk of pneumococcal disease. We compared incremental cost-effectiveness ratios from the schedule that was ultimately recommended with each potential simplified vaccination strategy.

Results: Most schedules analyzed resulted in several hundred additional deaths. While several possible schedules resulted in cost savings, these cost savings were modest compared to the health costs associated with them.

Conclusion: The schedule recommended by the ACIP in 2014, while complex, is the most health promoting compared to the modeled alternative schedules. The incremental cost-effectiveness ratio of the current schedule when compared to simplified alternatives is comparable to other vaccine-related interventions.

Keywords: Pneumococcal disease; Vaccination; Cost-effectiveness

Introduction

In 2014, a dose of 13-valent pneumococcal conjugate vaccine (PCV13) was added to the recommended schedule for adults age 65 years and older [1]. This was in addition to the previously recommended dose of 23-valent pneumococcal polysaccharide vaccine (PPSV23) for adults age 65 years and older as well as potentially two doses of PPSV23 for anyone over age 2 years that is in the population at increased risk for pneumococcal disease (IRPD). The pneumococcal vaccination schedule has been observed to be one of the most complicated schedules in the adult immunization program [2]. The adult pneumococcal schedule has two vaccines specified to occur in different timings at different ages, further there are different recommendations for each of three stratifications of risk level for pneumococcal disease (healthy, at increased risk, and immunocompromised) each of which has a different recommended vaccination schedule [3]. Complicated immunization schedules in children have been associated with increased office visits [4] leading to additional cost and inconvenience. In order to explore hypothetical simplified pneumococcal vaccination schedules for adults, we compared the health and economic consequences of the most recently recommended schedule with simpler schedules that did not include the risk-based recommendation for PPSV23 for adults without immunocompromising conditions. IRPD adults are defined to be adults: with long-term health problems, with conditions that lower the body's resistance to infection, that are taking treatments that lower the body's resistance to infection, that are smokers, or that have asthma [5]. We were asked by the pneumococcal working group to explore possible schedule changes that simplified the pneumococcal vaccination strategy. Some of the strategies explored the size of the disease increases if the IRPD recommendations were removed and others were designed to mitigate potential disease increases by shifting the recommended age for universal pneumococcal vaccination. Ultimately these alternative schedules were discarded by the pneumococcal working group as worse than the current complicated schedule. This study serves to document part of the evidence that decision was based on. We evaluated several hypothetical schedules that replaced the risk-based recommendation with earlier universal recommendations of PCV13 and/or PPSV23 at age 50 years.

Methods:

Model:

We developed a cohort model to estimate the cost-effectiveness of alternative pneumococcal vaccination schedules for adults that did not include specific recommendations for IRPD adults. We estimated medical and non-medical costs as well as disease burden using Monte Carlo simulation in spread sheet-based software [6].

We calculated invasive pneumococcal disease (IPD) and non-bacteraemia pneumococcal pneumonia (NBP) incidence as well as related deaths from age 50 through life expectancy or until age 100. We modelled these effects for schedules that recommended all adults receive (1) PCV13 at age 50, (2) PPSV23 at age 50, (3) PCV13 and PPSV23 at age 50, (4) PCV13 at age 65, (5) PCV13 and PPSV23 at age 65, (6) PCV13 at age 50 and PPSV at age 65, and (7) no vaccination. The baseline reference for each of these scenarios was the current pneumococcal schedule recommendation which calls for different vaccines at several different ages: a dose of PPSV23 at diagnosis of IRPD condition for age 50-64, a dose of PPSV23 five years after the diagnosis of the IRPD condition, a dose of PCV13 at age 65 (or 1 year later), and a dose of PPSV23 after the dose of PCV13 at age 65. Each of our modelled scenarios removed the recommendation for IRPD adults and many of our examined scenarios removed or modified the recommended ages for PCV13 and PPSV23. We calculated the incremental cost-effectiveness by subtracting total costs or health outcomes from the current recommendation. Our analysis was conducted from a societal perspective, which included all costs and benefits of vaccination.

Study population:

We analyzed the schedule impacts on a cohort the size of the 2013 United States population of 4,494,482 50 year-olds [7]. We excluded immunocompromised adults from this analysis as prior work indicates extremely high disease burdens among those groups makes targeted pneumococcal vaccination potentially cost-saving [8]. The remaining population was separated into IRPD and not IRPD populations. Adults with diabetes, chronic heart disease, chronic lung disease, and chronic liver disease were classified as IRPD.

Disease parameters:

We classified pneumococcal disease as vaccine type for PCV13 (serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F) and vaccine-type for PPSV23 (serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F and 33F). Risk, age, and serotype-specific rates of IPD were obtained from the Centers for Disease Control and Prevention's Active Bacterial Core surveillance (ABCs) in 2013. Age specific NBP rates were taken from published reports. Age and risk-specific disease rates are displayed in Table 1. In our model we projected these rates forward to account for the indirect protection provided by additional serotypes in PCV13 not covered by the 7-valent version [9-12].

Vaccine effectiveness and coverage:

We used estimates of PCV13 effectiveness against pneumococcal disease from the recently completed CAPiTA trial [13], and estimates of PPSV23 effectiveness from previous studies [14-17]. These vaccine effectiveness assumptions are detailed in Table 1. We assumed PCV13 waned by 10% every five years after age 65 and that PPSV23 wanted to 50% of initial effectiveness after five years, 30% after 10 years, and 0% after 15 years [15]. For each serotype subgroup, we assigned the cohort the most generous protection available from either PCV13 or PPSV23 after incorporating vaccine-specific waning effects.

Disease								
	Age 50-64, Healthy		**Age 50-64, IRPD**		**Age>65, Healthy**		**Age>65, IRPD**	
	base	**range**	**base**	**range**	**base**	**range**	**base**	**range**
IPD Rate (per 100,000)[a]	8.62	6.5-8.94	33.71	32.33-34.6	15.06	13.25-16.04	47.63	47.63-62.82
% IPD Cases Resulting in Fatality	6.74%		11.62%		11.85%		15.05%	
% PCV13 Serotype IPD	26.75		24.8		24.7		21.32	
% PPSV23 Serotype IPD	74.52		69.19		62.35		59.69	
% PPSV23 Serotype IPD (but not in PCV13)	48.09		44.39		38.06		38.37	
% Nonvaccine Serotype IPD	25.16		30.81		37.25		40.31	
Inpatient NBP Rate (per 100,000)[b]	258.2	258.2-267.7	258.2	258.2-267.7	1375.2	1375.2-1438.4	1375.2	1375.2-1438.4
% NBP Cases Resulting in Fatality[c]	3.2	2-4	3.2	02-Apr	6.7	5-7	6.7	5-7
Outpatient NBP Rate (per 100,000)[d]	600		600		2010		2010	
% NBP due to PCV13 typese	10		10		10		10	
Serotype changes between 2003 and 2009[a]								

(cases per 100,000)	Age 50-64, Healthy		Age 50-64, IRPD		Age>65, Healthy		Age>65, IRPD	
Year	2003	2009	2003	2009	2003	2009	2003	2009
PCV7 Types	6.26	1.34	6.26	1.34	13.62	1.82	13.62	1.82
PPSV23 Types not in PCV7	8.35	14.85	8.35	14.85	20.83	24.38	20.83	24.38
Types in neither PCV7 nor PPSV23	3.61	5.01	3.61	5.01	7.67	12.62	7.67	12.62
Vaccine Effectiveness								
	Age 50-64, Healthy		Age 50-64, IRPD		Age>65, Healthy		Age>65, IRPD	
	base	range	base	range	base	range	base	range
PCV *vs.* VT IPD[e]	75	41.43-90.78	75	41.43-90.78	75	41.43-90.78	75	41.43-90.78
PCV *vs.* VT NBP[e]	45	14.21-65.31	45	14.21-65.31	45	14.21-65.31	45	14.21-65.31
PPSV *vs.* VT IPD[f]	74	64-85	74	48-85	74	64-85	74	64-85
PPSV *vs.* VT NBP[g]	0	0-50	0	0-50	0	0-50	0	0-50
Vaccine Coverage								
	Age 50-64, Healthy		Age 50-64, IRPD		Age>65, Healthy		Age>65, IRPD	
	base	range	base	range	base	range	base	range
Coverage Rate (%)[h]	27.2	20-54.4	20	18.9-21.1	59.9	58.4-61.4	59.9	58.4-61.4
Cost per Case, 2010$[j]								
	Age 50-64, Healthy		Age 50-64, IRPD		Age>65, Healthy		Age>65, IRPD	
	base	range	base	range	base	range	base	range
IPD	40,161	31,950-49,086	40,161	31,950-49,086	27,097	21,981-32,695	27,097	21,981-32,695
Inpatient NBP	34,948	25,468-46,117	34,948	25,468-46,117	23,296	16,916-31,696	23,296	16,916-31,696
Outpatient NBP	127	77-219	127	77-219	254	121-463	254	121-463

Abbreviations: IRPD–Increased Risk for Pneumoccal Disease; IPD–Invasive Pneumococcal Disease; PCV13–13-valent Pneumococcal Conjugate Vaccine; PPSV23–23-valent Pneumococcal PolySaccharide Vaccine; NBP–Non-Bacteremic Pneumococcal Pneumonia; VT–Vaccine Type

[a]Source: ABCs surveillance data 2013 (9). Note inputs from ABCs are displayed here for reproducibility of final results. The number of digits displayed should not necessarily be construed as a measure of the accuracy of these outputs from ABCs surveillance data; [b]Source: Simonsen et al. 2014 (11); [c]Source: Huang et al. 2011; d Source: Nelson et al. 2008 (10); e Source: CAPITA; fSource: Moberley et al. 2008 (14); [g]Source: Fry et al. 2002 (15); [h]Source: National Health Interview Survey 2012 (18,19); jSource: MarketScan 2010 (22)

Table 1: Age and risk-specific disease rate, vaccine effectiveness, coverage rate, and cost inputs for prediction model

While coverage rates for IRPD 50-64 year olds and the population age 65 and older are available from the National Health Interview Survey [18], we made assumptions about coverage rates when modeling a universal recommendation for 50 year olds. We assumed coverage would be at least as high as in the IRPD population of 50-64 year-olds and no higher than the coverage rate for those 65 years and older after accounting for the high rate of doctor visits in the older age group [19]. We averaged these two bounds to arrive at the base case coverage rate for a universal recommendation for 50 year olds.

Health utility indices:

In order to aggregate morbidity and mortality from pneumococcal disease, we used quality-adjusted life year (QALY) decrements. A decrement of 0 indicates an individual in perfect health, while 1 indicates the individual is dead. We weighted published decrements for bacteremia and meningitis by case counts in 2013 ABCs surveillance data to arrive at an overall QALY decrement for IPD of 0.009 for healthy individuals. QALY decrements per acute instance of inpatient NBP (0.006) and outpatient NBP (0.004) for healthy individuals were

taken from previously published work. We multiplied these QALY decrements for individuals in perfect health by baseline risk and age specific QALY values to obtain appropriate QALY decrements for our cohort [20,21].

Medical and non-medical costs:

We averaged IPD (International Classification of Diseases, Ninth Revision, Clinical Modification codes 320.1, 038.2) and all-cause pneumonia (codes 481, 3.22, 11.6, 20.3, 20.4, 20.5, 55.1, 73.0, 112.4, 115.05, 115.15, 115.95, 130.4, 136.3, 480, 482, 483, 484, 485, 486, and 487.0) costs from the Truven Health Analytics MarketScan database 2010 separately for 50 through 64-year-olds and >65 year-olds. We used vaccine costs from government contract prices. After adjusting previously published estimates to 2013$, we calculated $23 for travel to a place of vaccine administration and $17 for the cost of vaccine administration itself. We adjusted all dollar values to 2013$ using the Consumer Price Index for all items. Health outcomes and costs were discounted by 3% [22-26].

Sensitivity analyses:

We used @Risk for Excel version 6.2.1 to obtain 95% confidence intervals. We conducted simulations until convergence had been achieved. Our stopping condition was that there was a 95% chance that the mean estimate of each output parameter was within 5% of its true value. We calculated the 5th and 95th percentiles of the sample mean for cost parameters in MarketScan by performing 1,000 bootstrap repetitions of calculating the mean with a sample size of 100. We then used these in a log-normal distribution function in our probabilistic sensitivity analysis. For the other parameters listed in Table 1, we used the maximum and minimum of the indicated range as minimum and maximum in Beta-pert distributions.

Results:

Results for the alternative schedules that exclude a IRPD specific recommendation for adults over age 50 are shown in Table 2. All analyzed schedules were health reducing in terms of QALYs compared to the ACIP-recommended schedule of PPSV23 for IRPD adults before age 65 years and PCV13 and PPSV23 at age 65. Three schedules that moved PCV13 to age 50 (PCV13 at 50, PCV13 at 50 and PPSV23 at 65, and PCV13 and PPSV23 at 50) reduced NBP cases and deaths at the cost of increasing IPD cases and deaths. Some schedules (PCV13 at 65 and PCV13 followed by PPSV23 at 65) had no impact on NBP cases and deaths in the base case, as our base case assumed PPSV23 had no effectiveness against NBP. Other schedules (no vaccination and PPSV23 at 50) resulted in increases in both IPD and NBP cases and deaths. Cost savings were greatest for the no vaccination strategy at $383 million, while the strategy that recommended both PCV13 and PPSV23 at age 50 was the most expensive costing a net $395 million compared to the current ACIP recommendation.

	None	PPSV23 at 50	PCV13 at 50	PCV13 at 65	PCV13 50 PPSV23 65	PCV13 and PPSV23 at 50	PCV13 and PPSV23 at 65
Health Outcomes							
IPD Cases	2,768	2,245	2,326	2,479	253	1,895	405
Hospitalized NBP Cases	1,858	1,858	-738	0	-738	-738	0
Non-hospitalized NBP Cases	2,715	2,715	-1,715	0	-1,715	-1,715	0
Deaths due to IPD	386	340	331	344	34	292	47
Deaths due to NBP	124	124	-24	0	-24	-24	0
QALYs	-4,027	-3,384	-2,339	-2,895	-4	-1,808	-560
Life-years	-6,469	-5,620	-3,956	-4,646	-129	-3,251	-819
Costs (million $)							
Total Cost	-$383	-$100	$108	-$117	$217	$395	-$8
Medical Costs	$133	$110	$43	$77	-$17	$25	$17
Vaccine Costs	-$516	-$210	$65	-$195	$234	$371	-$25
Cost Ratios ($)							
Cost/QALY	95,192	29,476	-46,011	40,490	-59925400	-2,18,513	13,964
Cost/Life-year	59,260	17,747	-27,205	25,229	-1683892	-1,21,567	9,539

Notes: Each value indicates the additional (if positive) or decreased (if negative) number of the indicated outcome when compared to the current ACIP recommended schedule for pneumococcal vaccination in adults. Current recommendations indicate a dose of PPSV23 at diagnosis of IRPD condition with another dose followed five years later. IRPD conditions include chronic heart disease, chronic lung disease, diabetes, cerebrospinal fluid leak, cochlear implants, alcoholism, chronic liver disease, or cigarette smoking. Current recommendations also indicate a dose of PCV13 at age 65 followed by a dose of PPSV23 [26]. The strategies here apply to all

adults (except the excluded immunocompromised) and indicate a universal dose of the specified vaccination at the specified age. All strategies are modeled with a cohort of 50 year olds.

Table 2: Health outcomes, costs, and cost ratios for vaccination scenarios compared to use of PPSV23 in IRPD adults 50-64 years and PCV13 and PPSV23 in all adults 65 years and older

Three schedules (PCV13 at 50, PCV13 at 50 and PPSV23 at 65, and PCV13 and PPSV23 at 50) were dominated–meaning they both increased costs and decreased QALYs. The remainder of the schedules decreased QALYs in exchange for some savings. The largest savings per QALY surrendered were from no vaccination, garnering $95,192 per QALY lost. The second most savings per QALY lost were in the PCV13 at 50 strategy that saved $40,490 per QALY lost.

Multivariate sensitivity analysis, shown in Table 3, displays the 95% confidence interval for each strategy. Generally, the 95% confidence intervals excluded zero. For instance, in each strategy save "PCV13 at 50 and PPSV23 at 65" the 95% confidence intervals are negative and exclude zero impacts on QALYs and zero impact on life-years. This indicates we can be relatively certain these strategies are health decreasing. While there is a 95% chance that the true life-year and QALY impacts for the "PCV13 at 50 and PPSV23 at 65" strategy are positive, this stragey also includes substantial total costs.

	No vaccines	PPSV23 at 50	PCV13 at 50	PCV13 at 65	PCV13 at 50 and PPSV23 at 65	PCV13 and PPSV23 at 50	PCV13 and PPSV23 at 65
Health Outcomes							
IPD Cases	(2,498, 3,204)	(1,979, 2,667)	(2,086, 2,757)	(2,244, 2,903)	(149, 312)	(1,644, 2,299)	(314, 455)
Hospitalized NBP Cases	(2,122, 11,435)	(1,442, 11,575)	(-568, 9,217)	(307, 9,882)	(-1,178, -297)	(-1,034, 8,649)	(8, 346)
Non-hospitalized NBP Cases	(3,210, 16,573)	(1,576, 16,478)	(-1,550, 12,806)	(525, 14,472)	(-2,715, -685)	(-2,748, 11,570)	(18, 800)
Deaths due to IPD	(348, 450)	(305, 404)	(298, 393)	(311, 406)	(23, 40)	(260, 352)	(36, 53)
Deaths due to NBP	(135, 724)	(109, 763)	(-11, 610)	(16, 635)	(-38, -9)	(-24, 593)	(0, 11)
QALYs	(-11,684, -4,623)	(-10,905, -3,413)	(-9,528, -2,386)	(-10,391, -3,253)	(-165, 639)	(-8,608, -1,436)	(-806, -495)
Life-years	(-14,680, -6,707)	(-14,068, -5,374)	(-12,486, -4,118)	(-13,215, -4,871)	(-424, 237)	(-11,405, -3,105)	(-1,033, -681)
Costs (million $)							
Total Cost	(-378, -110)	(-122, 158)	(109, 371)	(-109, 149)	(197, 235)	(376, 639)	(-11, 6)
Medical Costs	(138, 404)	(88, 368)	(43, 306)	(85, 343)	(-38, 1)	(3, 266)	(15, 31)
Vaccine Costs	(-519, -513)	(-213, -207)	(62, 68)	(-196, -193)	(232, 237)	(368, 376)	(-26, -24)
Cost Ratios ($)							
Cost/QALY	(9,576, 79,900)	(-15,105, 34,715)	(-51,214, -33,709)	(-14,664, 33,117)	(-6,568,471, 6,497,826)	(-265,001, -72,103)	(-7,877, 20,569)
Cost/Life-year	(7,201, 55,772)	(-11,552, 22,108)	(-33,589, -23,182)	(-11,447, 22,162)	(-6,984,252, 6,237,316)	(-123,577, -54,338)	(-6,148, 14,911)

Notes: Each value set indicates the upper and lower bounds of the 95% confidence interval for the indicated outcome when comparing the strategy indicated in the top row to the ACIP recommended schedule for pneumococcal vaccination in adults. Current recommendations indicate a dose of PPSV23 at diagnosis of IRPD condition with another dose followed five years later. IRPD conditions include chronic heart disease, chronic lung disease, diabetes, cerebrospinal fluid leak, cochlear implants, alcoholism, chronic liver disease, or cigarette smoking. Current recommendations also indicate a dose of PCV13 at age 65 followed by a dose of PPSV23 [26]. The strategies here apply to all adults (except the excluded immunocompromised) and indicate a universal dose of the specified vaccination at the specified age. All strategies are modeled with a cohort of 50 year olds.

Table 3: Sensitivity analyses for vaccination scenarios compared to use of PPSV23 in IRPD adults 50-64 years and PCV13 and PPSV23 in all adults 65 years and older

Discussion:

Removing the risk-based recommendation of receiving PPSV23 for IRPD immunocompetent adults over age 50 decreased health (in terms of total QALYs) for all vaccine schedules we examined. The dollars saved in total cost were small compared to the total health cost. The largest dollars saved per QALY lost were in a recommendation that removed all vaccinations for the general and IRPD populations over age 50. But this only returned $95,192 per QALY lost, which is less than the cost per QALY gained from many recent vaccine interventions.

The IPD incidence rate is approximately four times higher in IRPD 50-64 year olds than in the general population (Table 1), which makes targeting them with vaccination highly cost effective. The final column of Table 2 conducts the experiment of removing only the IRPD recommendation for 50-64 year olds while leaving the recommendations for adults age 65 years and older intact. While low coverage rates in the IRPD population suppress the total amount of additional cases and deaths from removing the IRPD specific pneumococcal vaccination, the resulting dollars saved is also very small. This results in a tiny savings per QALY given up.

There are several limitations to this study that must be acknowledged. First, indirect immunity for the newly covered serotypes in PCV13 are extrapolated forward from previous experience with PCV7. As adults are being immunized with PCV13 the portion of disease declines in adults due to direct immunization and indirect protection from the childhood program are indistinguishable. Second, we do not know coverage rates for a hypothetical universal vaccine recommendation for 50-64 year olds. We have instead extrapolated measured coverage rates from IRPD 50-64 year olds and the universal recommendation for 65 year olds.

While there was potentially substantial uncertainty surrounding the effectiveness of PPSV23 against NBP, a change in this value would not materially affect our results. Our strategies all involved removing PPSV23 for IRPD adults. As our conclusions indicate, this is a poor tradeoff based on PPSV23 effectiveness against IPD alone, so adding further consequences to these undesirable alternative schedules would not change our conclusion. We do note that the uncertainty surrounding the impact of PPSV23 on NBP does affect the size of the 95% confidence interval around NBP cases and any related outcomes.

While the adult pneumococcal schedule may be complicated, we find simplified schedules that omit the recommendation specific to adults at increased risk for pneumococcal disease are health decreasing. Further, the savings per QALY lost in these simplified schedules does not justify their health costs.

Author Contributions:

Conceived and designed the study: CS TP. Performed the analyses: CS LK RG. Analyzed the data: CS LK RG TP. Drafted the manuscript: CS TP. Reviewed the manuscript: CS LK RG TP.

Conflict of Interest:

The authors have no conflict of interest to declare.

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Ethics Statement:

The study did not involve patients or volunteers.

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