Pneumococcal Immunization

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Prepared by

Louise H. Anderson, PhD[2]

Michael V. Maciosek, PhD[1]

Nichol M. Edwards, MS[3]

Leif I. Solberg, MD[1]

Dana A. McGree[1]

Amy B. LaFrance, MPH[1]

HealthPartners Institute

[1]HealthPartners Institute
8170 33rd Avenue South
PO Box 1524, MS 23301A
Minneapolis MN 55440-1524
[2]Technomics Research LLC
[3]Contributed while employed by HealthPartners Institute

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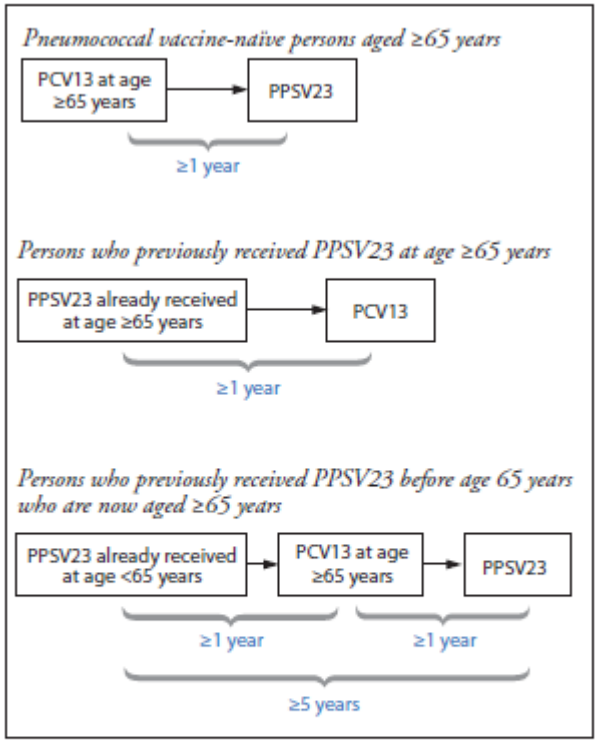
This report summarizes estimates of health impact and cost-effectiveness that were created to assess the relative value of most of the clinical preventive services recommended by the United States Preventive Services Task Force (USPSTF) and the Advisory Committee on Immunization Practices (ACIP). This ranking of clinical prevention priorities is guided by the National Commission on Prevention Priorities (NCPP).

A. ACIP Recommendation

The ACIP recommendation for persons aged 65 and older was updated in September 2015 to simplify the protocol.[1] (See Figure.) Now the ACIP recommends that both PCV13 and PPSV23 be given in series to adults in that age group. A dose of PCV13 should be provided initially and followed with a dose of PPSV23 at least one year later for immunocompetent adults ages 65 or older.[2] The vaccines should not be injected in the same medical visit. If a dose of PPSV23 is inadvertently administered earlier than the recommended interval, the dose need not be repeated.

BOX. Recommended intervals for sequential use of PCV13 and PPSV23 for immunocompetent adults aged ≥65 years — Advisory Committee on Immunization Practices, United States



Abbreviations: PCV13 = 13-valent pneumococcal conjugate vaccine; PPSV23 = 23-valent pneumococcal polysaccharide vaccine.
Notes: For adults aged ≥65 years with immunocompromising conditions, functional or anatomic asplenia, cerebrospinal fluid leaks, or cochlear implants, the recommended interval between PCV13 followed by PPSV23 is ≥8 weeks. For those for who previously received PPSV23 when aged <65 years and for whom an additional dose of PPSV23 is indicated when aged ≥65 years, this subsequent PPSV23 dose should be given ≥1 year after PCV13 and ≥5 years after the most recent dose of PPSV23.

Figure excerpted from Kobayashi et al. (2015).[1]

B. Choice of Population and Intervals

This evaluation focuses on vaccinations for the general population of persons age 65 and older. Vaccination of infants is included in our evaluation of the childhood immunization series. Younger adults and adults at high-risk are outside the scope of the Prevention Priorities project, which includes services for the general population and services that specifically target individuals at higher risk of cardiovascular disease or sexual transmitted infections. For the general population of adults age 65 and older, we treat pneumococcal vaccination as a one-time immunization series at or near the age of 65.

C. Model Type

The pneumococcal vaccination model is an aggregate cohort model based on spreadsheet calculations with some age-group and gender-specific calculations (as data permit) rolled into U.S. population results. However, as described below, more age-specific calculations underlie this update than in previous versions and thereby provide estimates that more closely approximate those from a microsimulation model.

This report represents a revision of an earlier model used to estimate the impact of one-time immunization of immunocompetent persons at age 65 with pneumococcal polysaccharide vaccine (PPSV23). The estimates were subsequently revised to reflect the August, 2014 update in ACIP recommendations to first vaccinate immunocompetent persons at age 65 with pneumococcal conjugate vaccine (PCV13), followed within 6-12 months with PPSV23.[3] For the update of these estimates, we added to our prior estimates of PPSV23 the incremental hospitalizations and deaths prevented by PCV13 as estimated by Stoecker.[4] We also updated cost estimates.

D. Literature Search and Abstraction

A literature search and abstraction were completed for the 2006 pneumococcal immunization model. An updated literature search and abstraction were completed in 2010 to update effectiveness and cost estimates. For the initial and update searches, we first identified articles for potential abstraction and, after reviewing them, we eliminated articles that did not meet our needs. Our criteria for eliminating articles, explained below for each literature search, were not pre-determined and were modified as the applicability of each study was determined. For the update to add the incremental impact of PCV13, we relied on estimates of Stoecker as indicated below and did not update our literature search.

D.1 Effectiveness Literature

We performed a Level 1 literature search[5] to identify articles that examined the effectiveness of the 23-valent pneumococcal polysaccharide vaccination. Our initial literature search identified articles in PubMed from January 1, 1992 through September 10, 2003. Examining these articles and the references of other articles identified, we found 17 articles for potential abstraction.[6-22] Of these 17 articles, 11 were abstracted. The remaining 6 articles were not abstracted because another article existed on the same study with longer outcomes,[8] the sample size was too small,[22] the outcome of interest had too few cases for analysis,[12] or the population was limited to those with chronic lung disease.[15-17]

We later performed a Level 1 literature search[5] to identify articles in PubMed that examined the effectiveness of the 23-valent pneumococcal polysaccharide vaccination and were published between September 1, 2003 and November 30, 2009. Examining these articles and the references of review articles, we found 5 articles to abstract.[23-27]

E. Clinically Preventable Burden (CPB) Estimate

CPB measures health impact. Conceptually, CPB is the burden addressed by the service multiplied by the effectiveness of the service. Table 1 shows the summary calculations for CPB. Some of the data points in Table 1 are estimates from the literature and others are calculated based on other data in the table. The "Data Source" column in Table 1 generally shows either the references for estimates or the formula used to calculate the variable using other data in the table. The letters in the formulas refer to the row labels (left-most column) for the data on which the calculation is based. The "Base Case" column shows the best available estimate for each variable used in our calculation of CPB, and the "Range" column shows the range over which the point estimates were varied in our sensitivity analyses.[4] We created

additional tables (not shown) to summarize the evidence and perform supporting calculations. Their contents are described below.

F. Burden of Disease

F.1 Bacterial Pneumococcal Mortality (rows a-f)

CPB was based on delivery of the service to a one-year U.S. birth cohort (the size of which was defined consistently for NCPP analyses as 4 million) over the age range for which the service was recommended by the USPSTF. Pneumococcal mortality (row a) was estimated from case fatality rates among persons above the age of 65 as reported in the 2009 Active Bacterial Core Surveillance (ABCs) Report on Streptococcus pneumoniae.[28] Age group-specific death rates were needed to accurately estimate the numbers of deaths that would occur over the lifetime of a birth cohort, and were provided by personal communication with CDC.[29] We used the 2011 U.S. Life Tables in calculations requiring life expectancy estimates.[30] The number of pneumococcal deaths in a birth cohort of 4 million individuals was estimated and stratified by 10-year age groups for age 65 and older. The total number of invasive pneumococcal disease (IPD) deaths in a birth cohort of 4 million individuals aged 65 and older was calculated at 4,456 (row a).

This estimate approximates cumulative (lifetime risk) IPD deaths among persons aged 65 and older in the birth cohort, given current vaccination practices. To estimate the total value of pneumococcal vaccination, we first predicted what the burden would be in the absence of vaccination among older adults by adjusting for current vaccination rates.

The CDC's Behavioral Risk Factor Surveillance System (BRFSS) reported that 62.3% of individuals aged 65 and older had been immunized in 2001; the rate increased slowly to 65.9% in 2005, was level at about 67% in years 2006-2008, and reached 68.5% in 2009.[31] BRFSS median rates by age group in years 2006-2008 were about 60% for ages 65-74 and 75% for ages 75 and above, increasing slightly to 61.8% and 76.7% in 2009. A study by Jackson et al. reported patterns of pneumococcal vaccination in a cross-section of managed care organization (MCO) members.[32] Among adults aged 65 or more, 82% had received at least one pneumococcal vaccination, a higher overall percentage than that reported by the BRFSS survey, which may be due to the insured status of the study population, the administrative data source used for vaccination history, and the systems in place at the MCOs to improve immunization delivery rates. Jackson et al. also analyzed the rate of pneumococcal vaccination by five-year age group. They found that 67% of 65-69 year-olds and 83%-88% of the older age groups had received at least one vaccination, a similar pattern by age as that reported by BRFSS. We based our estimate of the current delivery rate on the BRFSS median rate by age group because we judged the BRFSS rates to be more representative of the national average. Our current vaccination rates were 62% for 65-74 year-olds and 77% for ages 75 and above, for an overall current rate of 67.4% for the U.S. population (row b). In sensitivity analysis, our low estimate was 80% and our high estimate was 110% of the base rates.

The efficacy estimate used in the estimation of deaths in the absence of vacciatation (row f) is explained below in section E.2 in the discussion of efficacy and effectiveness. Using the calculation shown for row f, we estimated that 5,410 invasive pneumococcal disease deaths would occur among individuals age 65 and older in the absence of vaccination. This calculation is based on algebraic manipulation of the expression: (deaths observed) = (deaths without vaccine) x (1- delivery rate) + (deaths without vaccine) x (delivery rate) x (1 - efficacy), where the additive components represents deaths among those who did not receive vaccination plus deaths among those who did receive vaccination respectively.

F.2 Bacterial Pneumococcal Hospitalizations (row g-k)

The calculation of IPD hospitalizations in the absence of vaccination is similar to that of prevented pneumococcal mortality. Because most cases of IPD among the adults aged 65 and above result in hospitalization,[33] we used the case rate from the 2009 Active Bacterial Core Surveillance Report on *Streptococcus pneumoniae* as the rate of IPD hospitalizations for the total vaccinated and unvaccinated population.[28] Given current vaccination practices, we predicted 25,739 hospitalizations would occur over the lifetime of a birth cohort of 4 million (row g). In the absence of vaccination, we estimated that 32,449 invasive pneumococcal disease hospitalizations would occur over their lifetime (row k).

F.3 Effectiveness of Vaccination

The primary distinction we make between efficacy and effectiveness is that effectiveness reflects the level of patient adherence that can be expected in everyday practice, while efficacy reflects 100% patient adherence.[5] CPB is based on effectiveness and therefore, the potential health benefits to individuals who fail to accept the service when offered are not included in CPB.

F.4 Effectiveness Literature for PPSV23

We abstracted 16 articles that examined the effectiveness of pneumococcal vaccination.[6,7,9-11,13,14,18-21,23-27] As part of the 2006 literature review, we examined articles on both the 14- and 23-valent vaccines in an effort to find estimates of vaccine effectiveness against mortality. However, because the current recommendation is for the 23-valent vaccine, articles that did not examine the efficacy of the 23-valent vaccine were not included in our estimate of the effectiveness of pneumococcal vaccination.[10,14,20] In addition, three studies were excluded after abstraction: the study by Wagner et al. was excluded because the study outcome was pneumonia, not IPD; and the studies by Benin et al. and Musher et al. were excluded because the populations were not generalizable.[6,21,25]

F.5 Efficacy of PPSV23 in reducing death

Only one article reported the efficacy of the 23-valent vaccine in reducing deaths from IPD. Hedlund et al.[11] found a 47% reduction in in-hospital deaths from IPD. Hedlund et al. used administrative ICD codes to identify cases of IPD, which leaves some risk for underestimating vaccine effectiveness due to misclassification, and, although the study population was more than 250,000 subjects, the number of deaths was very small. Three studies (inclusive of one study that was ultimately excluded –Wagner et al.) reported the efficacy of the 23-valent vaccine in reducing deaths from pneumonia or pneumococcal infection. Wagner et al.[21] found a 67% reduction in deaths in an Austrian nursing home population. Generalizability to the U.S. population aged 65 and older (both community-living and living in extended-care facilities) may be limited. Christenson et al.[23] found a 35% reduction in pneumonia deaths among hospitalized subjects vaccinated with the pneumococcal and influenza vaccine and a 7% reduction among subjects who had received the pneumococcal vaccine only. Vila-Corcoles et al.[26] found a 50% reduction in deaths due to pneumococcal infection and a 59% reduction in deaths due to pneumonia. None of these three studies measured the efficacy of the vaccine in preventing deaths from IPD, which is a rare event. Therefore, because evidence of IPD mortality reduction was very limited, we used the estimate of morbidity reduction as our estimate of efficacy against deaths (row e). In doing so, we implicitly assumed that the case fatality rate for patients with IPD is the same for those with and without prior vaccination.

There is scant evidence of the effect of prior vaccination on case fatality rates for patients with IPD. One study of HIV-infected IPD patients found that those with prior vaccination had reduced in-hospital mortality;[34] however, generalizability of those results to the general population ages 65 and over is questionable. Other studies examining the protective benefits of prior vaccination for patients with

community-acquired pneumonia have found mixed results. [35-37] Because evidence to support reduced case rate mortality among vaccinated IPD patients is lacking, we assumed the rate to be the same for those with and without prior vaccination.

F.6 Efficacy of PPSV23 in reducing hospitalizations for IPD (rows c and h)

Nine studies provided estimates of vaccine efficacy against IPD.[9,11,13,18,19,23,24,26,27] Only one of these studies was a randomized controlled trial: Ortqvist et al. found a 21% reduction in risk of developing bacteremic pneumococcal pneumonia.[18] In a retrospective cohort study, Jackson et al. found a 46% risk reduction of pneumococcal bacteremia in immunocompetent patients.[13] Three prospective cohort studies reported vaccine efficacy: Christenson et al. reported 73% vaccine efficacy in reduction of hospital admissions for IPD in Sweden.[23] Also in Sweden, Hedlund et al. reported efficacy of 48% in reducing yearly hospital admissions for IPD.[11] In Spain, Vila-Corcoles et al. reported efficacy of 40% in reducing hospitalizations for IPD.[26] Four case-control studies also reported vaccine efficacy: Dominguez et al. found 70% vaccine efficacy against IPD in Spain;[24] Farr et al. reported finding 81% efficacy in the prevention of pneumococcal bacteremia hospitalizations;[9] Shapiro et al. found the efficacy of the vaccine to be 47% against all proven pneumococcal hospitalizations, regardless of serotype;[19] and Vila-Corcoles et al. found 66% vaccine efficacy in preventing bacteremic pneumococcal pneumonia hospitalizations in Spain.[27] The mean vaccine efficacy for prevention of IPD hospitalizations caused by all serotypes reported in these articles was 62% (median 66%).

However, the studies had significant limitations for our purposes. The Farr et al. study included subjects aged 2+, with an average case age of 58.2 years. The Hedlund et al. and Christenson et al. studies used administrative ICD codes to identify cases of IPD, which had the potential to understate vaccine effectiveness through misclassification. More importantly, most of the studies did not analyze vaccine efficacy by interval after vaccination, and there is some evidence that vaccine efficacy declines with duration.

Two studies did report vaccine efficacy by interval from vaccination. Shapiro et al.[19] found that vaccine efficacy decreased as age at vaccination increased or interval from vaccination increased. In contrast, a study by Butler et al.[7] found no decrease in vaccine efficacy as the interval from vaccination increased in observations with a maximum of 11 years from vaccination to onset of illness. Both studies measured vaccine efficacy against serotypes found in the vaccine. To be conservative in our estimate of CPB, we based our vaccine efficacy on Shapiro et al. Our base case estimate of vaccine efficacy for vaccine serotypes was 80% at age 65, decreasing linearly to 0% at age 90. In sensitivity analysis, we followed Sisk et al.[38] for our low estimate by defining effectiveness to be 80% at age 65, decreasing linearly to 58% five years later and 0% thereafter; and our high estimate was 80% for all ages. Our base case estimate yielded a lifetime average vaccine efficacy in reducing IPD deaths of 34.9% (row c) and lifetime vaccine efficacy in reducing IPD hospitalizations of 40.9% (row h). As stated above, we used the same underlying estimate of vaccine efficacy for deaths as for hospitalizations; however it is important to note that the efficacy and effectiveness estimates reported in Table 1 reflect lifetime estimates that have been weighted by age-specific incidence of IPD hospitalizations and death. Because the rates of death increase with age **faster** than the rates of hospitalizations increase with age andour estimate of vaccine efficacy **decreased** with age, the lifetime average vaccine efficacy for preventing deaths was lower than the lifetime average vaccine efficacy for preventing hospitalizations.

F.7 Vaccine serotype coverage of PPSV23 (rows d and i)

Because our estimate of vaccine efficacy was for serotypes found in the vaccine, we incorporated an estimate of the percent of cases caused by serotypes in the vaccine. Several sources offered estimates

of serotype coverage before the introduction of the 7-valent pneumococcal conjugate vaccine (PCV7). Shapiro et al.[19] reported that 89% of cases (vaccinated and unvaccinated) were infected with a serotype represented in the 23-valent vaccine, and 93% of cases were infected with a vaccine-serotype or one related to a vaccine-serotype. Butler et al.[7] reported that 88% of unvaccinated patients were infected with serotypes included in the 23-valent vaccine. In cost-effectiveness modeling, Sisk et al.[38] assumed 88% serotype coverage, the mid-point between 84% of unvaccinated patients having serotypes represented in the 23-valent vaccine and 93% which were in the vaccine or vaccine-related based upon serotype coverage percentages from CDC unpublished data. Another cost-effectiveness model from Smith et al.,[39] also using data from the CDC, assumed serotype coverage percentages that varied by age, ranging from 77% for ages 65-69 to 70% for ages 85 and above. Finally, the ACIP, in its 1997 recommendation,[40] stated that the 23-valent vaccine represents 85%-90% of the serotypes that cause IPD among children and adults in the United States.

PCV7 was introduced in late 2000 for children younger than age five and ACIP recommended its use among children 2 to 5 years old at increased risk. In 2008 ACIP extended its recommendation to include all children 2 to 5 years old[41], and updated its recommendation to use of the PCV13 vaccination when it was licensed in 2010[42]. Childhood pneumococcal vaccinations have had a dramatic impact on the incidence and serotypes of IPD cases for adults ages 65 and over. An analysis using 2007 data reported that the percentage of IPD cases among vaccinated and unvaccinated individuals caused by serotypes in the PPV23 vaccine was 64.7%.[33] From this number, we estimated that 75% of IPD cases among the unvaccinated population were of the 23-valent serotypes by accounting for vaccine efficacy and the percentage of the population that was vaccinated. Therefore we used 75% as our base case estimate for vaccine serotype coverage (rows d and i); we used 65% and 85% in sensitivity analysis. Vaccine efficacy for all serotypes (rows e and j) resulted from multiplying efficacy for vaccine serotypes only by the vaccine serotype coverage percentage.

F.8 Patient Adherence (rows l- m)

From studies of interventions to increase uptake of vaccinations, we calculated total uptake among those who either were found to be vaccinated upon assessment for study eligibility or who had received vaccinations after being offered the vaccine during the study. In university and VA outpatient clinics, 79% and 76% of patients were up-to-date following intervention.[43,44] More recent results from a managed care organization found that 89% of eligible members were vaccinated after a telephone intervention [45] and 88% of patients in clinic study accepted vaccination after nurse or physician recommendation.[46] With multiple opportunities to be vaccinated at or shortly after age 65, we assumed 90% would accept the vaccine by age 70 (row l). Our range in sensitivity analysis captures slightly lower rates of getting patients being up-to-date either before or as the result of one-time interventions in two inpatient studies.[47,48] Based on these data, we assumed 90% of adults 65 years of age would accept offers to be vaccinated with PCV13. Among those who accepted PCV13, we assumed 95% would subsequently be vaccinated with PPSV23 (row m).

F.9 CPB Estimate (row y)

With 5,410 deaths predicted in the absence of the vaccine (row f), and 22% effectiveness of the PPSV23 vaccine after accounting for non-adherence (row n), 1,210 deaths would be prevented by offering the PPSV23 to average risk individuals at age 65 (row p). Stoecker estimated that an additional 365 deaths from IPD and nonbacterial pneumonia would be prevented with the addition of PCV13 in a current cohort of 65 year-olds.[4] After adjusting this estimate for the size of the birth cohort used to standardize our analyses across preventive services (4,000,000) and for non-adherence with vaccination, we added 308 additional deaths prevented from first vaccinating with PCV13(row q). Average life expectancy at

death from pneumococcal disease is approximately 12.41(row r) years.[49,50] Therefore, an estimated 18,873 years of life would be gained (row y).

Similarly, 8,509 hospitalizations would be avoided by vaccination with PPSV23 alone (row t). We added 4,379 additional prevented IPD and nonbacterial pneumonia hospitalizations from first vaccinating with PCV13 based on Stoecker's estimate after adjustment for birth cohort size and vaccine adherence, (row u).[4] Based on the duration of illness for equally disabling conditions, we assumed an average duration of illness of 3 weeks, or 0.058 years (row v). We used our standard quality-of-life reduction estimates for acute conditions: 0.30 QALYs per year (row w). Using these averages in the calculation shown for row x, 223 additional years of healthy life equivalents would be gained (row x).

CPB is the sum of the quality adjusted life years (QALYs) from the mortality and morbidity prevented in a birth cohort of 4 million individuals, which for this service is 18,873 QALYs saved (row y).

F.10 Sensitivity Analysis for CPB

In single-variable sensitivity analysis, we find CPB to be most sensitive to changes in the efficacy of the vaccine in preventing IPD caused by serotypes in the vaccine. Over the range specified in section E.2.2 for this variable, CPB falls 28.6% and increases 71.4%. CPB is also moderately sensitive to estimates of pneumococcal mortality in a birth cohort (row a), average years of life lost to pneumococcal death (row p), percent of serotype coverage (row d), and the low estimate of adherence (row m). Changes to each variable changes CPB by 15%-43.5%.

Following our methods,[5,51] we conducted multivariate sensitivity analysis to determine the three variables which, when changed together, produced the highest and lowest estimates of CPB. Simultaneously changing efficacy of the vaccine for vaccine serotypes along with any two of the estimates for pneumococcal mortality, average years of life lost to pneumococcal death, or vaccine serotype coverage over the ranges specified in Table 1 produced a CPB range of 5,722 to 64,229 QALYs saved.

G. Cost-effectiveness Estimate

We estimated cost-effectiveness based on our CPB as presented in Table 2, which has the same format as Table 1. We continued our lettering for row labels from Table 1 because the CE estimate is built on the data points presented in Table 1. Some of the entries in the data source column in Table 2 refer to rows of Table 1.

A complete birth cohort approach requires year-by-year modeling and discounting of future benefits back to a single base-year; typically, the first year the preventive service is offered to the birth cohort (in this case, age 65). We discounted the future years of life saved from a death prevented, QALYs saved from hospitalizations prevented, and costs of hospitalizations to their present value in the year in of vaccination. All discounting was at 3% annually.

G.1 Cost Savings from Vaccinations (rows z-bb)

We used Smith et al.'s[39] cost-effectiveness study as one source for IPD treatment cost variables. Their estimates are based on analysis of Health Care Utilization Project (HCUP) data. Stoecker provides a second set of estimates based on MarketScan data[4]. Because within-study differences by age group or type of pneumococcal disease hospitalization were small, we created an overall weighted average of pneumonia hospitalization costs within-study (averaged across age groups in the case of Smith et al. and

averaged across IPD versus nonbacterial pneumonia the case of Stoecker), and then inflation-adjusted and averaged the results from the two sources to get the average cost of a hospitalized case $20,185, shown in row z. Total cost-savings of $260.2 million in 2012 dollars were the result of multiplying age-specific deaths prevented by cost per fatal case and age specific hospitalizations prevented by cost per case discharged alive (row aa). We discounted the cost-savings from the year incurred to the year of vaccination (age 65), resulting in discounted hospitalization cost-savings of $215.1 million (row bb).

G.2 Vaccination Costs (rows cc-ff)

To approximate the resource cost of vaccination we use an average of estimates of private sector and Medicare payments. This average provides a proxy for real resource use, and is used across other preventive services in the priorities ranking. Private sector costs were estimated as the average of CDC private sector cost per dose of 10-dose vials,[52] plus 75% of the median charge for vaccine administration CPT4 code 90741.[53] In 2012, the Medicare payment limit for PPV13 was $137, while PPSV23 was $66.[54] Medicare reimbursement for vaccine administration in 2012 was $24.[56] The average of private sector and Medicare costs, inclusive of vaccine administration are shown in rows cc and dd.

We used our standard method for valuing patient time for an office visit: 2 hours travel and visit time, valued by average hourly earnings in 2012(row ee)[57]. As with other services that are likely to be delivered during visits at which other services are provided, we assigned only a portion of patient costs for travel and visit attendance to the pneumococcal vaccination. Because vaccination is relatively simple, and side-effects requiring medical attention are rare, we assumed 10% of patient time for an office visit would be used for vaccination. We assumed that three-quarters of patients receive a pneumococcal vaccination during a visit when other services are provided, and for the remainder, vaccination is the sole reason for the visit. Our estimate was, on average, that 33% of patient time for an office visit was used for vaccination. (row ff).

Total lifetime vaccination costs for the birth cohort of four million were $839.8 million in 2012 dollars (row gg). Because these costs occur in the first year, discounting is not necessary.

G.3 Discounting and CE Calculation (rows hh-oo)

Net costs from offering pneumococcal vaccine to a birth cohort of four million at age 65 were $624.7 million (row hh).

We used present value calculations to estimate the average present value of years of life gained. At a 3% discount rate, the 12.29 years of life per death prevented (row r), had a present value (in the year the service is provided) of 8.45 years (row jj). Applying the same quality-of-life estimates, duration-of-illness estimates, vaccination efficacy, and adherence as used for CPB, yielded 13,977 discounted life years saved from prevented deaths (row kk) and 223 discounted QALYs from prevented hospitalizations (row ll), for a total of 14,200 discounted QALYs saved over the remaining years of a birth cohort's life (row mm).

Dividing net costs by QALYs saved yielded a CE ratio of $43,992 per QALY saved (row nn). Net costs per vaccination were $217.88 (row oo).

G.4 Sensitivity Analysis for CE

In single-variable sensitivity analysis, we find CE to be most sensitive to changes in the efficacy of the vaccine in preventing IPD caused by serotypes in the vaccine as well as duration of the protection

conferred by the vaccine. Over the range specified in section E.2.3 for this variable, the CE ratio falls 55.7% and increases 59.9%. CE is also sensitive to estimates of the cost of the vaccine, the serotype coverage, pneumococcal mortality, average years of life lost to pneumococcal death, and patient time cost. Changes to each variable changes the CE ratio by 25-40%.

We explored combinations of the variables listed above in multivariate sensitivity analyses to find the combination of three variables that produce the lowest and highest CE estimates.[51] Simultaneously changing the efficacy of the vaccine in preventing IPD caused by serotypes in the vaccine, the cost of the vaccine, and the serotype coverage produced our lower bound estimate of $4,925 saved per person vaccinated. Simultaneously changing vaccine efficacy, serotype coverage, and pneumococcal mortality produced a CE ratio of $138,926 per QALY saved.

H. Limitations

Our models provided transparent estimates of the benefits and CE of offering pneumococcal vaccine to a birth cohort of 4 million individuals starting at the age of 65. Like all models, the accuracy of our estimate is limited by the accuracy of the most influential data points. We found some of the most uncertain data points to be the most influential, including patient time costs to receive the vaccine, the efficacy of the pneumococcal vaccine in preventing mortality, the mortality incidence, and the years of life gained per death prevented. These data points were either not directly observed or were observed in populations that may not be generalizable to the target population across the United States.

In addition to usual limitations of data inputs, our update to incorporate PCV13 vaccination relies on prevented deaths and hospitalizations of another model that uses similar, but not identical, data sources.[4] Therefore some internal inconsistencies between our estimates for the impact of PPSV vaccine and the incremental value of the PCV13 are inevitable. It seems unlikely that these inconsistencies would result in estimates outside our ranges for sensitivity analysis. Finally, Stoecker estimated the number of non-hospitalized nonbacterial pneumonia cases prevented by PCV13.[4] For simplicity, we did not incorporate non-hospitalized, nonbacterial pneumococcal cases because we determined they would change both CPB and CE by less than 1 percent.

Table 1. Summary of CPB Estimate for Pneumococcal Vaccination (Adults Age 65 and Older)				
Row	**Variable**	**Base Case**	**Data Source**	**Range for Sensitivity Analysis**
	Number of 65-year-olds in a birth cohort of 4 million	3,353,483	[30]	
a	Total IPD mortality in a birth cohort of 4 million age 65 and older	4456	[28,49,58,59]	+/-20%
b	Current vaccination rate	67.4%	[32,60]	54%-74%
c	Weighted lifetime efficacy of vaccine in reducing IPD deaths, vaccine serotypes only	34.9%	[7,19]	see text
d	Vaccine serotype coverage	75%	See text on Pilishvili	65%-85%
e	Weighted lifetime efficacy of vaccine in reducing IPD deaths – all serotypes	26.2%	c*d	
f	Predicted deaths in the absence of vaccination	5,410	a/(1-b*e)	
g	Total IPD hospitalizations in a birth cohort of 4 million age 65 and older	25,739	[28,59]	+/-20%
h	Weighted lifetime efficacy of vaccine in reducing IPD hospitalizations – vaccine serotypes only	40.9%	[7,19]	see text
i	Vaccine serotype coverage of PPSV23	75%	d	
j	Weighted lifetime efficacy of of PPSV23 in reducing IPD hospitalizations – all serotypes	30.7%	h*i	
k	Predicted hospitalizations in the absence of of PPSV23 vaccination	32,449	g/(1-b*j)	
l	% of patients accepting PCV13	90%	[43-48]	75%-95%
m	% of patients accepting PPSV23 among those accepting PCV13	95%		
n	Weighted lifetime effectiveness of PPSV23 vaccination in preventing IPD deaths	22%	e*l*m	
o	Weighted lifetime effectiveness of PPSV23 vaccination in preventing IPD hospitalizations	26%	j*l	
p	Number of IPD deaths prevented from PPSV23	1,210	f*n	
q	Incremental IPD and NPB deaths prevented from PCV13	308	See text on Stoecker	
r	Average life years lost per IPD death	12.29	[49,50]	+/-20%
s	Number of life years saved	18,650	(p+q)*r	
t	Number of pneumococcal hospitalizations prevented from PPSV23	8,509	k*o	
u	Incremental IPD and NPB hospitalizations prevented from PCV13	4,379	See text on Stoecker	
v	Duration of illness (years)	0.058	=3/52	1 to 5 weeks
w	QALY weight	0.30		0.2 to 0.4
x	Number of QALYs saved	223	(t+u)*v*w	
y	Total QALYs saved from deaths and hospitalizations **(CPB estimate)**	**18,873**	s+x	

Table 2. Calculation of Cost Effectiveness of the Pneumococcal Vaccine Being Offered to a Birth Cohort of 4 million at Age 65.				
Row	**Variable**	**Base Case**	**Data Source**	**Range for Sensitivity Analysis**
	Health care cost savings			
z	Cost per inpatient stay	$20,185	[39]	+/- 25%
aa	Total hospitalization savings from PCV13 and PPVS23	$260,159,171		
bb	Discounted hospitalization cost savings from PPSV23	$215,115,877		
	Vaccination costs			
cc	PCV13 costs including vaccine administration	$157	see text	
dd	PPSV23 cost including vacation administration	$89	see text	
ee	Office visit patient time and travel costs (2 hours total)	$62	[61]	+/- 50%
ff	Portion of office visit for vaccination	33%	see text	+/- 25%
gg	Lifetime vaccination costs	$839,825,744	(dd+ee*ff)*m *age 65 population	
	Cost Effectiveness			
hh	Net costs	$624,709,866	gg-bb	
ii	Discount rate	3%	see text	
jj	Average present value of LY saved per death from year of immunization	8.45	see text	
kk	Discounted LY saved from PCV13 and PPSV23	13,977	p*jj	
ll	Discounted QALYs saved from prevented hospitalizations from PCV13	223	see text	
mm	Discounted QALYs saved from PCV13 and PPSV23	14,200	jj+kk	
nn	Cost Effectiveness	43,992 $/QALY saved	hh/mm	
oo	Net costs per full vaccination	$218	hh/(m*age 65 population)	
(Note: All costs in 2012 dollars.)				

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