

Pneumococcal Immunization: Technical Report Prepared for the National Commission on Prevention Priorities

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A. ACIP Recommendation

The Advisory Committee on Immunization Practices (ACIP) recommends that the pneumococcal polysaccharide vaccine be used more extensively, and be administered to all persons in the following groups: a) persons aged greater than or equal to 65 years, b) immunocompetent persons aged greater than or equal to 2 years who are at increased risk for illness and death associated with pneumococcal disease because of chronic illness, c) persons aged greater than or equal to 2 years with functional or anatomic asplenia, d) persons aged greater than or equal to 2 years living in environments in which the risk for disease is high, and e) immunocompromised persons aged greater than or equal to 2 years who are at high risk for infection.^{1;2}

B. Choice of Population and Intervals

This evaluation focuses on vaccinations for the general population of persons age 65 and older. ACIP also recommends vaccination for infants and younger adults at high risk of complications from pneumonia. Vaccination of infants is included in our evaluation of the childhood immunization series. Younger 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. The frequency at which people should receive the pneumococcal vaccine is unclear due to limited information on long-term efficacy of the vaccine. ACIP recommends that persons age 65 and older be revaccinated only when two conditions are met: they last received the vaccine before age 65 and were last vaccinated 5 or more years ago. Therefore, for the general population of adults age 65 and older, we treat pneumococcal vaccination as a one time immunization at or near the age of 65.

C. Literature Search and Abstraction

C.1 Effectiveness Literature

We performed a Level 1 literature search³ to identify articles that examined the effectiveness of the 23-valent pneumococcal polysaccharide vaccination. Our 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.⁴⁻²⁰ 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,¹⁸ the sample size was too small,¹⁷ the outcome of interest had too few cases for analysis,¹⁶ or the population was limited to those with chronic lung disease.^{9;14;15}

C.2 Cost Effectiveness Literature

We performed a Level 1 literature search³ to identify cost effectiveness literature. Articles from PubMed were identified, and 14 cost effectiveness articles on pneumococcal vaccination were obtained for potential abstraction.²¹⁻³⁴ Only one of these articles was suitable for abstraction.³¹ The other 13 articles were not abstracted because they were not analyzed in the US health care setting using US dollars, the age group analyzed was not 65 years and older, they evaluated a military population, or they evaluated outreach programs.

D. Clinically Preventable Burden (CPB) Estimate

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 upon other data in the table. The “Data Source” column in Table 1 shows either the references for estimates or the formula used to calculate the variable. 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 that was used in our calculation of CPB, and the “Range” column shows the range over which the point estimates were varied in our sensitivity analyses.³ We created additional tables (not shown) to summarize the evidence and perform supporting calculations. Their contents are described below.

D.1 Burden of Disease:

D.1.1. Pneumococcal Mortality: Rows a-d.

CPB is based on delivery of the service to a one-year U.S. birth cohort (the size of which is defined consistently in this study as 4 million) over the age range for which the service is recommended by the USPSTF. Pneumococcal mortality (row a) was estimated from total deaths among persons above the age of 65 as reported in the 2000 Active Bacterial Core Surveillance (ABCs) Report on *Streptococcus pneumoniae*.³⁵ Age group-specific death rates are needed in order to accurately estimate the numbers of deaths that would occur over the lifetime of a birth cohort, and ABCs does not report age subgroups within the age 65 and older group. Therefore, we distributed the deaths found in ABCs using death rates for more specific age groups in 1998 as reported in the Compressed Mortality File³⁶ for deaths with ICD-9 code 481. Whenever U.S. population estimates were needed for calculations, 2000 census data were used.³⁷ 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 deaths in a birth cohort of 4 million individuals age 65 and older was calculated at 6,920 (row a).

This estimate approximates cumulative (lifetime risk) pneumococcal deaths among persons age 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 by adjusting for current vaccination rates. Death rates in 2000 (row a) would have been impacted by vaccination rates at that time. In 2001, 62.3% of individuals age 65 and older had been immunized, and this rate increased slowly to 64.7% in 2004.³⁸ We used an estimate of 62% for vaccination status in 2000 (row b).

The efficacy estimate used in the calculation shown for row c is explained below in section D.2 in the discussion of efficacy and effectiveness. Using the calculation shown for row d, we estimated that 10,520 pneumococcal 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 (efficacy). See the methods technical report for additional details.³⁹

D.1.4. Pneumococcal Hospitalizations: Row e-g.

The calculation of invasive pneumococcal hospitalizations in the absence of vaccination is similar to that from prevented pneumococcal mortality. As a measure of invasive pneumococcal hospitalizations, we used information from the 2000 Active Bacterial Core

Surveillance Report on *Streptococcus pneumoniae*.³⁵ As with mortality, hospitalizations were estimated by age group over the lifetime of a birth cohort of 4 million. The result is predicted lifetime hospitalizations among individuals age 65 and older in the absence of vaccination: 33,811 hospitalizations in a birth cohort of 4 million (row e). We estimated that 51,403 pneumococcal hospitalizations (row g) would occur among individuals age 65 and older in the absence of vaccination.

D.2 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.³ CPB is based on effectiveness and therefore, the potential health benefits to individuals who either fail to accept the service when offered or to adhere with follow-up treatment or advice to change behavior are not included in CPB.

D.2.1 Effectiveness Literature:

We abstracted eleven articles that examined the effectiveness of pneumococcal vaccination.^{4-8;10-13;19;20} We examined articles that determined the efficacy of both the 14 and 23-valent vaccines to try to obtain mortality information. None of the 14-valent articles abstracted contained information on the effectiveness of the vaccine against mortality. Since 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.^{5;6;8;12} In addition, the study by Benin et al. was excluded because it only reported effectiveness against serotypes included in the vaccine, and therefore the results could not be paired with our burden estimate to calculate CPB.⁴

D.2.2. Efficacy of Vaccination: Rows c and f.

Only one article reported the efficacy of the 23-valent vaccine in reducing deaths from pneumonia.¹³ This study found a 67% reduction in deaths in an Austrian nursing home population. Generalizability to the U.S. population age 65 and older (both community-living and living in extended care facilities) may be limited. There were 6 studies that provided estimates of effectiveness against pneumococcal disease^{7;10;11;13;19;20} Wagner et al. reported a 72% reduction in the risk of pneumonia in a Austrian nursing home population.¹³ Jackson et al. found a 54% risk reduction of pneumococcal bacteremia in immunocompetent patients.⁷ Ortvist et al. found a 22% reduction in risk of developing pneumococcal pneumonia.¹⁰ In a case-control study by Shapiro et al., they found the effectiveness of the vaccine to be 47% against all proven pneumococcal infections, regardless of serotype.¹¹ Farr et al. reported finding 81% efficacy in the prevention of pneumococcal bacteremia.¹⁹ Finally Hedlund et al reported a 48% reduction in the incidence of yearly hospital admissions for invasive pneumococcal disease. The mean efficacy of these articles in preventing pneumococcal disease was 55% (median 54%). Due to the limited generalizability of the single estimate of mortality reduction, we used the more conservative estimate of morbidity reduction for both efficacy against hospitalizations (row f) and deaths (row c).

D.2.3. Patient Adherence: Row h.

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 89% of patients were up-to-date following intervention.^{40;41} With multiple opportunities to be vaccinated, we assumed 90% would accept the vaccine by age 70 (row h), and no additional individuals would accept the vaccine after age 70. 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.^{42;43}

D.3 CPB Estimate: Row r

With 10,520 deaths predicted in the absence of the vaccine (row d), and 47% effectiveness of the vaccine after accounting for non-adherence (row j), 5,226 deaths would be prevented by offering the vaccine to average risk individuals beginning at age 65. Average life expectancy at death from pneumococcal disease is approximately 6.9 years.^{36;44} Therefore, an estimated 35,977 years of life would be gained.

Similarly, 25,537 hospitalizations would be avoided (row n). Based upon the duration of illness for equally disabling conditions, we assumed an average duration of illness of 3 weeks, or 0.058 years (row o). We used our standard quality of life reduction estimates for acute conditions: 0.30 QALYs per year (row p). Using these averages in the calculation shown for row q, 442 additional years of healthy life equivalents would be gained (row q).

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: 36,419 QALYs saved (row r).

D.4 Sensitivity Analysis for CPB

In single variable sensitivity analysis, we find CPB to be most sensitive to changes in the efficacy of vaccination in preventing pneumococcal deaths. Over the range specified in Table 1 for this variable, CPB falls 25% and increases 47%. CPB is also moderately sensitive to estimates of pneumococcal mortality in a birth cohort (row a) and to average years of life lost to pneumococcal death (row l). Changes to each variable changes CPB by about 20%.

Following our methods,^{45;46} we conducted multivariate sensitivity analysis to determine the three variables which, when changed together, produce the highest and lowest estimates of CPB. Simultaneously changing the three variables noted above over the ranges specified in Table 1 produces a CPB range of 17,500 to 76,900 QALYs saved.

E. Cost Effectiveness Estimate

Sisk et al. have estimated the CE of pneumococcal immunizations for adults in a Markov model using methods consistent with reference case of the Panel on Cost-effectiveness in Health and Medicine (PCEHM).^{31;47} Their study poses three challenges in creating an estimate that can be reliably compared to other services in our analysis of prevention priorities. First, the analysis was performed in 1993 dollars, and inflation adjustment over long periods may introduce substantial error. Second, the ACIP recommendation implies that average risk adults should be vaccinated one-time shortly after turning age 65, while Sisk et al. reported results for the cross-section of adults age 65 and older and subpopulations age 65-74, 75-84 and 85 and older. The results of each of these cross-sections have potential limitations when used to represent cost-effectiveness in a birth cohort who are offered screening starting at age 65. Third, Sisk et al. conservatively assumed the vaccine's effectiveness lasted only 6 years while ACIP recommends one-time vaccination for average risk adults based on indirect evidence of longer lasting protection.

Our decision to use the results of Sisk et al. rather than develop a new estimate was based on two considerations. First, our methods limit the potential for error in inflation adjustment by using a base year of 2000, so that older studies need less inflation adjustment than if we had used a more current comparison year. Second, Sisk et al. found cost-savings in each age group they analyzed and the differences in results between groups were small even though incidence of pneumococcal disease increases with age. Therefore, we chose to use the results in the cross-section of all adults age 65 and older. Relative to a birth cohort, the cross-sectional approach discounts future benefits less than the birth cohort approach, making the service appear more cost-effective. However, because benefits of vaccination were limited to 6 years in the model, the effect of the differential in discounting is smaller than if longer vaccine effectiveness durations were used, and the conservative nature of the 6-year assumption balances the favorable effect of discounting. While a model based on a birth-cohort approach using longer vaccine effectiveness durations would yield a somewhat different estimate, we judged it extremely unlikely that it would change the score for the service. Our full sensitivity analysis (see below) ultimately confirmed this.

Rows a-f of Table 2 show the base case results for the age 65 and older group from Sisk et al. Because discounted net costs are negative ($\$96.69 - \$88.42 = -\$8.27$), the CE ratio is not defined. Therefore the base case results for Sisk et al. is a cost-savings of \$8.27 per person vaccinated in 1993 dollars, discounted to present value at rate of 3% per year. When adjusting to year 2000 dollars using the Medical Consumer Price Index (MCPI) as shown in rows g-k, we calculated a net savings of \$10.71.

Sisk et al. did not incorporate the time costs of patients as needed for the societal perspective. As shown in rows l-r, we added these using our standard method for valuing patient travel to an office visit: 2 hours travel and visit time, valued by average hourly earnings in 2000.⁴⁸ As with other services which are likely to be delivered during visits at which other services are provided, we assign 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 only 10% of patient time for an office visit would be used for vaccination. Because these costs occur in the first year, discounting is not necessary. Thus \$4.23 is added to net costs, reducing net savings to \$6.48 per person immunized in year 2000 dollars (row q).

E.3 Sensitivity Analysis for CE

In single variable sensitivity analysis, net costs changed by 30% with changes to the inflation index; by 50% with changes to net costs of vaccination (tabulated by simultaneously changing both total costs with and without vaccination); by 50% with changes to value of patient time (row l); and by up to 95% with changes to the portion of an office visit attributable to vaccination. In all cases, vaccinations remained cost-savings.

We did not explore changes in QALYs saved in single variable sensitivity as part of the CE sensitivity analysis as net costs were negative and QALYs saved were independent of net costs in our calculations. Within the original model, changes to variables such as disease incidence and vaccine effectiveness would simultaneous affect net costs and QALYs saved. Our secondary analysis of this study cannot estimate these effects. However, the changes in QALYs would only be explored in the CE ratio and the CE ratio would be undefined unless the change in incidence or effectiveness produced net costs that were positive.

For the Prevention Priorities project, we summarized multivariate sensitivity analysis by reporting the results of the widest range obtained by simultaneously changing combinations of three variables. When using existing cost-effectiveness studies to estimate CE, the multivariate estimate was limited by the detail of reporting of the study. In most cases, this required us to limit reporting of multivariate sensitivity analysis to simultaneous changes in two highly aggregated estimates such as net costs and net QALYs. For this service, we were able to maintain the standard of using three variables by including the CPI index and our two variables for patient time costs in sensitivity analysis. Unlike the single variable sensitivity analysis, net QALYs come into play in multivariate sensitivity analysis because simultaneous changes of two variables impacting costs did produce positive net costs whereas by themselves, they did not.

When exploring less cost-effective scenarios in multivariate sensitivity analysis, CE ratios up to 1,400 \$/QALY were obtained by changing (in different combinations of 3) net costs, net QALYs, the price index, the value of patient time, and portion of a 10 minute office visit that is attributable to vaccination. Savings (negative net costs) as high as \$12 per person was obtained by changing variables in the other direction.

F. Scoring

We ranked services in the Prevention Priorities Project based upon scores for CPB and CE rather than point estimates.^{3:39} For each measure, we assigned scores according to the quintile in which the service's CPB and CE estimates fell among all services included in the study scope. Services having the highest CPB or best-cost-effectiveness received a score of 5 and the worst a score of 1.

The base case estimate of 36,419 QALYs saved resulted in a CPB score of 3. Sensitivity analysis revealed several scenarios in which CPB would have received a score of 2. Sensitivity analysis revealed no scenarios in which CPB would have received a score of 1, 4 or 5.

In the base case, pneumococcal vaccinations for adults produces cost-savings, but produces the least cost-savings among 6 services that produce cost-savings and no scenarios in multivariate sensitivity analysis produced enough savings to move the service into the 5th spot. Therefore the base case CE score for this service is a 4 and no scenarios were identified that would produce a CE score of 5. The highest CE ratio obtained was 1,400 \$/QALY saved, which also would keep the CE score at a 4. Thus, pneumococcal vaccinations for adults have an unusually stable CE score.

G. Limitations

Our simplified 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 which may not be generalizable to the target population across the United States. Taking into account the uncertainty of these data points and adjusting them in sensitivity analysis showed that the overall score of this service could only change by 1 point, and this change was caused in the CPB estimate, as sensitivity analysis on CE was shown to be extremely stable.

Table 1. Summary of CPB Estimate for Pneumococcal Vaccination (Adults Age 65 and Older)				
Row	Variable	Base Case	Data Source	Range for Sensitivity Analysis
a	Total pneumococcal (invasive) mortality in a birth cohort of 4 million age 65 and older	6,920	35;44	+/-20%
b	% receiving pneumococcal vaccination	62%	38	55%-70%
c	Efficacy of vaccine in reducing pneumococcal deaths	55%	7;10;11;13;19;20	45%-70%
d	Predicted deaths in the absence of vaccination	10,520	$a/(1-b*c)$	
e	Total pneumococcal (invasive) hospitalizations in a birth cohort of 4 million age 65 and older	33,811	35;44	+/-20%
f	Efficacy of vaccine in reducing pneumococcal hospitalizations	55%	7;10;11;13;19;20	
g	Predicted hospitalizations in the absence of vaccination	51,403	$e/(1-b*f)$	
h	% of patients accepting vaccination	90%	40;41	75%-95%
i	Effectiveness of vaccination in preventing pneumococcal deaths	47%	$c*h$	
j	Effectiveness of vaccination in preventing pneumococcal hospitalizations	47%	$f*h$	
k	Number of pneumococcal deaths prevented	5,452	$d*i$	
l	Average life years lost per pneumococcal death	6.88	44	+/-20%
m	Number of life years saved	35,977	$k*l$	
n	Number of pneumococcal hospitalizations prevented	25,537	$g*j$	
o	Duration of illness (years)	0.06		1 to 5 weeks
p	QALY weight	0.30		0.2 to 0.4
q	Number of QALYs saved	442	$n*o*p$	
r	Total QALYs saved from deaths and hospitalizations (CPB estimate)	36,419	$m+q$	

Table 2. Adjusted CE Ratio for 1-Time Pneumococcal Vaccination of Average Risk Adults (Age 65 and Older)				
Row	Variable	Base Case	Data Source	Range for Sensitivity Analysis
Summary of published estimate				
a	Total cost, no vaccine	\$96.69	³¹	+/-25%
b	Total cost, vaccine	\$88.42	³¹	+/-25%
c	QALYs, no vaccine ages	6.22478	³¹	+/-25%
d	QALYs, vaccine ages	6.22811	³¹	+/-25%
e	Net cost per person vaccinated	-\$8.27	b-a	
f	Published average CE ratio	Not defined	(b-a)/(d-c)	
Adjustment to year 2000 dollars				
g	Inflation index from 1993 to 2000	1.295	MCPI	1.10 to 1.50
h	Total cost, no vaccine, \$2000	\$125.21	a*g	
i	Total cost, vaccine, \$2000	\$114.50	b*g	
j	Net cost per person vaccinated	-10.71	i-h	
k	Adjusted average CE ratio	Not defined	(i-h)/(d-c)	
Adjustment for patient time costs				
l	Patient time and travel per visit	\$42.32	⁴⁸	+/- 50%
m	Portion of office visit for vaccine	10%	assumed	5% to 20%
n	Patient time cost for vaccine	\$4.23	l*m	
o	Total cost, no vaccine, \$2000	\$125.21	h	
p	Total costs, vaccine, \$2000 with patient time	\$118.73	i+n	
q	Net cost per person vaccinated	-\$6.48	p-o	
r	Adjusted average CE ratio	Not defined	(p-o)/(d-c)	

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