Meningococcal Immunization

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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 Advisory Committee on Immunization Practices (ACIP) recently updated recommendations for use of the quadrivalent meningococcal conjugate vaccines.(1) The ACIP recommends routine vaccination with a quadrivalent meningococcal conjugate vaccine for all 11- or 12-year-olds, with a booster dose at age 16.

B. Choice of Population and Intervals

This evaluation focuses on vaccinations for the general population of persons aged 11 and older. Children 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 sexually transmitted infections. Following the ACIP recommendation, we treat meningococcal vaccination as a two-time immunization, with the first dose at age 11 and the booster at age 16. Our model projects invasive meningococcal disease (IMD) cases, deaths, and cases with long-term sequelae for a birth cohort of 4 million aged 11 through 34, the ages at which the recommended for meningococcal vaccine is expected to be effective against IMD. We use rates of incidence caused by serogroups C, Y, and W-135, the three serogroups occurring in the United States and included in the recommended quadrivalent conjugate vaccine.

C. Model Type

In previous iterations of the Prevention Priorities work, most models were relatively simple compartmental models These are spreadsheet-based calculations with some age-group and gender-specific calculations, as data permit, rolled up into U.S. population results. Many services are now being updated to either Markov or agent-based micro-simulation models and incorporating race/ethnicity and socioeconomic status when feasible. At this time, the meningococcal model is a compartmental model. However, as described below, age-specific calculations underlie this model where appropriate and yield results consistent with simulation models.

D. Literature Search and Abstraction

We performed a literature search to identify articles that examined the effectiveness and cost-effectiveness of the quadrivalent meningococcal conjugate vaccine. Our literature search identified articles in PubMed through May, 2011. The first quadrivalent meningococcal conjugate vaccine was licensed in the U.S. in 2005 and recommended by ACIP for routine use in that year.(2) We identified few published estimates of the vaccine's effectiveness and only early estimates of its long-term effectiveness.(3; 4) However, we found three detailed cost-effectiveness articles and we used these as foundations for our estimates.(5-7)

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 were estimates from the literature and others were 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.(8) We created additional tables (not shown) to summarize the evidence and perform supporting calculations. Their contents are described below.

E.1 Burden of Disease (rows c-e)

CPB was based on delivery of the service to a one-year U.S. birth cohort (the size of which was defined consistently in this study as 4 million) over the age range for which the service was recommended by the USPSTF or ACIP. Invasive meningococcal disease cases (row c) were estimated from the average case rate per 100,000 for the years 1991 through 2002 for age groups 10-13, 14-17, 18-24, and 25-64 from the Centers for Disease Control's Active Bacterial Core Surveillance (ABCs).(7) These were case rates of IMD incidence in absence of vaccine because the polysaccharide vaccine available during those years was not recommended for routine use.(9; 10) The number of IMD cases in a birth cohort of 4 million individuals aged 11 through 34 was calculated as 534 (row c), and overall incidence rate of 0.56 per 100,000.

IMD deaths were estimated from age-group specific case fatality ratios (CFRs) calculated from ABCs.(7) The age groups were 11-17, 18-22, 23-32, and 33-64. The number of deaths due to IMD in a cohort of 4 million individuals aged 11 through 34 was 55, a CFR of about 10% (row d).

The percentage of non-fatal cases of IMD that result in long-term sequelae were estimated using references cited by Shepard et al.(6) and Ortega-Sanchez et al.(7) Following their methods, we assumed that the conditions were mutually exclusive. We summed the probabilities for all conditions and used 20% as our estimate of the percentage of non-fatal IMD cases would result in long-term sequelae.

Long-term sequelae outcomes and probabilities		
Sequelae	Percentage of non-fatal cases	Reference
Skin scarring	7.6%	Erickson and De Wals, 1998(11)
Single amputation	1.9%	Erickson and De Wals, 1998(11)
Multiple amputation	1.2%	Erickson and De Wals, 1998(11)
Hearing loss	6.4%	Baraff et al., 1993(12)
Neurologic disability	2.1%	Baraff et al., 1993(12)
Total	19.2%	

In absence of vaccine, 96 of the 534 cases would result in long-term sequelae (row e).

E.2 Efficacy of vaccination in reducing IMD (row f)

The ACIP Meningococcal Vaccines Work Group recommended a booster dose at age 16, after initial vaccination at age 11 or 12, based on epidemiological data indicating that the vaccine might not protect adolescents for more than five years.(1) An early study estimated vaccine efficacy of 80% to 85% up to three years after vaccination.(3) Preliminary results from a case-control study that began in 2006 showed vaccine efficacy of 95%, 91%, and 58% for persons vaccinated less than one year, one year, and two through five years earlier, respectively, with an overall rate of 78%.(1) A simulation study recently reported estimates of vaccine efficacy within three to four years after vaccination at 80% to 85%.(4)

The cost-effectiveness studies we used as foundations for our work based their vaccine efficacy estimates on meningococcal serogroup C conjugate vaccine efficacy observed in the United Kingdom. In their base case scenario, Shepard et al. assumed initial vaccine efficacy for adolescents of 93%, reduced by 25% ten years after vaccination to recognize waning of vaccine-induced immunity.(6) Ortega-Sanchez et al. assumed 93% vaccine efficacy over a ten-year time period.(7)

We assumed a vaccine efficacy of 93% for ten years, which reflects the high vaccine efficacy expected after initial vaccination and continuing high efficacy after the booster vaccination at age 16. Vaccine efficacy after ten years is unknown, so we followed the method of Shepard et al. and reduced efficacy by 25%, resulting in 70% efficacy for durations eleven and after. Over the lifetime modeled, vaccine efficacy was 83% (row f).

E.3 Patient Adherence (row g)

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.(8) 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.

Patient adherence is the percentage of patients who would accept vaccination if it were offered by their doctor during an office visit. We were unable to find estimates of patient adherence for meningococcal vaccine. However, estimates of vaccination coverage were available. The National Immunization Survey–Teen estimate of the percentage of adolescents aged 13 to 17 who had received at least one dose of the quadrivalent meningococcal conjugate vaccine was 41.8% in 2008, and increased to 53.6% in 2009.(13)

We used results from studies of patient adherence to other preventive services for adolescents and young adults as indicators of patient adherence for meningococcal vaccination. Rand et al. surveyed girls and their parents in Monroe County, New York by telephone to measure acceptance of human papillomavirus vaccine.(14) They reported 75% acceptance. Pimenta et al. reported 76% and 84% acceptance of non-invasive screening for chlamydial infection in health care settings from two study sites in England.(15) We define adherence as acceptance of vaccination when it is offered in a clinician's office. We assume patients are more likely to accept vaccination in that setting, so we used the higher patient adherence rate of 85% (row g).

E.5 CPB Estimate (rows h-s)

With lifetime vaccine efficacy of 83% and patient adherence of 85%, 378 cases of IMD would be prevented if the vaccine were offered at ages 11 and 16 to a birth cohort of 4 million (row h). We assumed that all IMD cases would result in hospitalization. We based our estimate for length of stay of nine days on a study of meningococcal hospital cases.(16) We used our standard quality-of-life adjustment for acute conditions, 0.30 QALYs reduction per year, to estimate a saving of three QALYs from prevented hospitalizations (row k).

Using the same efficacy and adherence assumptions, we estimated that 39 deaths would be prevented by offering the vaccine to a birth cohort of 4 million (row l). The average life years lost per death was 60.3 years (row m), yielding 2,955 life years saved from prevented deaths (row n). Life expectancy estimates were from the 2004 U.S. Life Tables.(17)

Similarly, 68 cases with long-term sequelae would be prevented (row o). We assumed reduced quality of life for cases with long-term sequelae for their remaining life expectancy and estimated a saving of 612

QALYs from prevented cases with sequelae (row r). We assumed that the life expectancy for cases with long-term sequelae was the same as for the general population, but quality of life would be reduced. Our QALY reduction was 0.15, averaged over individual sequelae condition QALY reductions and weighted by the probability of the condition occurring. Our estimate of the annual QALY reduction associated with skin scarring of 0.0 (no loss of health-related quality of life) was the same as that used by Shepard et al.(6; 18) Our estimate of the annual QALY reduction associated with neurological disability of 0.45 was from The Global Burden of Disease DALY estimate for mental retardation.(19) Our estimate of annual QALY reduction associated with hearing loss, single amputation, and multiple amputations was based on our standard estimate for chronic conditions. We assumed an annual QALY reduction of 0.20 for hearing loss and single amputation and a reduction of 0.30 for multiple amputations.

Total QALYs saved from offering meningococcal vaccine at ages 11 and 16 were 2,905 (row s).

E.6 Sensitivity Analysis for CPB

In single-variable sensitivity analysis, we found CPB increased or decreased by 20% with changes in either the case incidence rate or life expectancy variables. CPB increased or decreased by 12% to 15% with changes in the case fatality rate, vaccine efficacy, adherence, and quality of life reduction for cases with long-term sequelae. Following our methods(20), we conducted multivariate sensitivity analysis to determine the three variables which, when changed together, produced the highest and lowest estimates of CPB. Simultaneously changing case incidence rate, case fatality rate, and life expectancy over the ranges specified in Table 1 produced a CPB range of 1,892 to 4,255 QALYs saved.

F. Cost Effectiveness Estimate

We used three previously published cost-effectiveness analyses as foundations for our work, but they posed challenges in creating a CE estimate that could be reliably compared to other services in our analysis of prevention priorities. Scott et al. estimated cost-effectiveness of routine vaccination of a cohort of first year, dormitory-living college students over a four-year time frame.(5) That study wasn't applicable to our work for a number of reasons. First the study population didn't match the population ACIP recommended for routine meningococcal vaccination. Second, the vaccine evaluated was the polysaccharide quadrivalent vaccine, not the recommended conjugate vaccine. Third, the study time-frame was four-years, appropriate for vaccination of college students with the polysaccharide vaccine, but not applicable to a study of adolescents routinely vaccinated at age 11 or 12, followed by a booster dose at age 16.

Ortega-Sanchez et al. estimated the cost effectiveness of a catch-up campaign for adolescents aged 11-17, followed by routine vaccination for children aged 11.(7) They modeled a population of 10 million with the age distribution equal to the entire U.S. population. Using evidence from the U.K., they incorporated herd immunity into their model. Our prevention priorities analyses consistently define the study population as a birth cohort of four million.

Shepard et al.'s study was the most applicable to our work, but it, too, offered challenges. The authors compared costs and benefits of a no vaccine strategy to a routine vaccination strategy at age 11 for a hypothetical U.S. cohort. The study assumed a single dose of the conjugate vaccine and estimated effects over a 22 year time-frame. Benefits included reduced morbidity and mortality from cases of IMD and associated long-term sequelae; treatment cost savings including parent care-giving time and public health response; and productivity savings. Costs of vaccinations included vaccine costs and cost of adverse events. Several of the study's assumptions were inconsistent with our needs. First, the study did

not include a booster vaccination at age 16. Second, the study included parent care-giving time for cases of IMD, but did not include the value of parent time in the cost of the vaccination. Third, the study included the costs of public health response. The published study did not provide enough detail for us to adjust its results to create estimates that would be consistent with estimates of other services for the NCPP.

We produce a CE estimate based on our CPB estimate to provide a clear, updated estimate of CE that was methodologically comparable to the CE estimate of other services evaluated in this study, and to provide full sensitivity analysis. We present our estimate in Table 2, which has the same format as Table 1. We continued our lettering for row labels from Table 1. Some of the entries in the data source column in Table 2 refer to rows of Table 1. All dollar amounts are inflation-adjusted to 2012 dollars.

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 11. We discounted the future health impacts and costs to present value at age 11 with a 3% annul discount rate.

F.1 Cost Savings from Vaccinations

Cost savings resulted from prevented cases of IMD and their associated hospitalization costs and prevented cases with long-term sequelae and their associated treatment costs. We used O'Brien et al.'s health care costs, inflated to 2012 using the medical care CPI, for our estimate of $37,957 per case (row t).(16) Total hospitalization cost savings from prevented cases were $14.3 million (row u). Discounted to the age at which the service was first offered, age 11, at 3% per year, hospital cost savings were $11.4 million (row v).

Our estimate of lifetime treatment costs for cases with long-term sequelae was $308,100 per case and was developed by averaging long-term costs from individual sequelae conditions, weighted by the probability of the condition occurring (row w). We used Shepard et al. to identify sources for our estimates of costs for the individual sequelae conditions and inflated costs to 2012 dollars. Costs and components for each sequelae condition are below.

Long-term treatment costs for cases with sequelae			
Sequelae	Long-term cost	Components	Reference
Skin scarring	$8,279	• Acute treatment	Scott et al., 2002(5)
Single amputation	423,888	• Acute treatment • One temporary below knee prosthesis • Permanent below knee prosthesis, including modifications, replaced every four years for 50 years • Annual maintenance	Williams, 1994(21)
Multiple amputation	508,665	• Single amputation cost x 120%	Shepard et al., 2005(6)
Hearing loss	95,861	• Cochlear implant; pre-, operative, and post- costs;	Cheng et al., 2000(22)

		and follow-up	
Neurologic disability	1,820,625	• Incremental cost of mental retardation special education for 10 years	Chambers et al., 2003(23)
		• Average of intermediate residential care facility and home- and community- based services cost per resident for 50 years	Chapter 7 in Alba et al., 2008(24)
Weighted average	$308,100		

Total treatment savings from prevented cases with long-term sequelae were $20.9 million (row x). Discounted savings were $16.6 million (row y). Total savings from prevented cases was $35.2 million (row z); total discounted savings were $28 million (row aa).

F.2 Vaccination Costs

Our estimate of the health sector cost of vaccination was developed by adding vaccine costs from the CDC Vaccine Price List of December 2012 to the cost of vaccine administration. The CDC Vaccine Price List for meningococcal conjugate vaccine was $82.12 for the CDC cost per dose and $110.19 for private sector cost per dose.(25) We allocated 53% of doses to the CDC cost and 47% to private sector cost, based on analyses by Zhou et al.(26) Vaccine administration cost was $17.55, based on a 0.75 costs-to-charges ratio.(26) The total vaccine cost was $112.86 (row bb).

We used our standard method for valuing patient time for an office visit: two hours travel and visit time, valued by average hourly earnings in 2012. For our model of meningococcal vaccine offered to adolescents, we assumed parents accompanied the adolescents to the visit and valued the parent time. We did not value the adolescent time. We used average hourly earnings plus benefits in 2005(27) to estimate the value of parent time at $31 per hour in 2012 dollars (row cc). Because some patients receive one or more other services at a visit, we assumed that half of the office visit time is attributable to the vaccination (row dd).

Total lifetime vaccination costs for the birth cohort of four million were $970.4 million (row ee). Vaccination costs were $903.8 million after discounting to the first year the service was offered (row ff).

F.3 Discounting and CE Calculation

Discounted net costs from offering meningococcal vaccination to a birth cohort of four million at ages 11 and 16 were $875.8 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 59.5 years of life per death prevented (row m), had a present value (in the first year the service was offered) of 22.8 years (row ii). Applying the same quality-of-life estimates, duration-of-illness estimates, vaccination efficacy, and adherence as used for CPB, yielded 886 discounted life years saved from prevented deaths (row jj), 2 discounted QALYs from prevented hospitalizations (row kk), and 231 discounted QALYs from prevented cases with long-term sequelae (row ll), for a total of 1,119 discounted QALYs saved over the years from the modeled ages of 11 through 34.

Dividing discounted net costs by discounted QALYs saved yielded a CE ratio of $782,602 per QALY saved (row nn). Discounted net costs per vaccination were $129.84 (row oo).

F.4 Sensitivity Analysis for CE

In single variable sensitivity analysis, we found CE most sensitive to changes in the case incidence rate, life expectancy, and vaccine cost variables. CE increased or decreased by 17% to 26% with changes in those variables. CE was also sensitive to changes in the case fatality rate, value of parent time to receive the vaccine, and the quality of life reduction for cases with long-term sequelae. CE increased or decreased by 11% to 18% with changes in those variables. Following our methods(20), we conducted multivariate sensitivity analysis to determine the three variables which, when changed together, produced the highest and lowest estimates of CE. Simultaneously changing case incidence rate, life expectancy, and vaccine cost produced CE ratios of $430,000 to $1.5million per QALY saved.

G. Limitations

Our model provides transparent estimates of the benefits and CE of offering quadrivalent conjugate meningococcal vaccine to a birth cohort of 4 million individuals at ages 11 and 16. Like all models, the accuracy of our estimate is limited by the accuracy of the most influential data points. Our estimates of CBP and CE were most sensitive to the incidence case rate, case fatality rate, life expectancy and vaccine cost.

Our estimate of vaccine efficacy relies on early reports of vaccine efficacy and previously published cost-effective analyses. The estimate of efficacy five years beyond the initial or booster vaccination is uncertain. Sensitivity analysis indicated that vaccine efficacy was in important variable, but not as significant as case incidence rate, case fatality rate, or vaccine cost.

Updates performed in 2015 were limited to inflation adjustments. Therefore more up-to-date findings from peer-reviewed published literature following the initial analysis and prior to the inflation adjustment were not incorporated into this report.

Table 1. Summary of CPB Estimate for Meningococcal Vaccination (Ages 11 through 34)				
Row	**Variable**	**Base Case**	**Data Source**	**Range for Sensitivity Analysis**
a	Number of 11-year-olds in a birth cohort of 4 million	3,969,147	(17)	
b	Number of 16-year-olds in a birth cohort of 4 million	3,966,147	(17)	
c	Predicted cases in absence of vaccine	534	(7)	+/-20%
d	Predicted deaths in absence of vaccine	55	(7)	+/-20%
e	Predicted cases with long-term sequelae in absence of vaccine	96	(11; 12)	+/-20%
f	Lifetime effectiveness of vaccine	83%	(6)	80% to 98% yrs 1-10
g	% of patients accepting vaccination	85%	(14; 15)	75% to 95%
h	Number of cases prevented	378	c*f*g	
i	Length of hospitalization (years)	0.025	(16)	5 to 21 days
j	QALY weight	0.30	see text	0.20 to 0.40
k	QALYs saved from prevented cases	3	h*i*j	
l	Number of deaths prevented	39	d*f*g	
m	Average life years lost per death	60.3	(7; 17)	+/-20%
n	Life years saved from prevented deaths	2,955	l*m	
o	Number of sequelae cases prevented	68	e*f*g	
p	Life expectancy with sequelae	59.5	(17)	+/-20%
q	QALY weight	0.15	(18; 19) see text	0.10 to 0.25
r	QALYs saved from prevented sequelae cases	612	o*p*q	
s	Total QALYs Saved (CPB estimate)	2,905	k+n+r	

Table 2. Calculation of Cost Effectiveness of the Meningococcal Vaccine (Ages 11 through 34)				
Row	**Variable**	**Base Case**	**Data Source**	**Range for Sensitivity Analysis**
	Health care cost savings			
t	Cost per case, hospitalization	$37,957	(16)	+/-25%
u	Total hospitalization case savings	$14,342,230	h*t	
v	Discounted hospitalization case savings	$11,381,938	see text	
w	Cost per case with long-term sequelae	$308,100	(5; 6; 21-24)	+/-25%
x	Total long-term sequelae savings	$20,892,789	o*w	
y	Discounted long-term sequelae savings	$16,571,435	see text	
z	Total savings	$35,235,019	u+x	
aa	Discounted total savings	$27,953,373	v+y	
	Vaccination costs			
bb	Per vaccination health care costs	$112.86	(38; 39)	+/-25%
cc	Per office visit parent time and travel costs ($31/hour for 2 hours)	$62	(27)	+/-25%
dd	Portion of office visit for vaccination	50%	see text	33% to 67%
ee	Lifetime vaccination costs	$970,406,118	(a+b)*g*(bb+cc*dd)	
ff	Discounted vaccination costs	$903,764,331	see text	
	Cost effectiveness			
gg	Net costs	$935,171,099	ee-z	
hh	Discounted net costs	$875,810,958	ff-aa	
ii	Average discounted value of LY saved per prevented death	22.8	see text	
jj	Discounted LY saved	886	l*ii	
kk	Discounted QALYs from prevented hospitalizations	2	see text	
ll	Discounted QALYs from prevented long-term sequelae	231	see text	
mm	Total discounted QALYs saved	1,119	jj+kk+ll	
nn	Cost effectiveness	$782,602	hh/mm	

oo	Discounted net costs per vaccination	129.84	hh/((a+b)*g)	

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