

Influenza Immunization for Adults 50 Years and Older: 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 annual influenza vaccinations for adults 50 or more years of age as part of the adult immunization schedule.^{1;2}

B. Variation in Influenza Seasons

The severity of influenza and the degree of antigenic match of the influenza vaccine vary from year to year; as a result, the CPB and CE of influenza vaccinations may vary significantly over time. We aimed to create CPB and CE estimates which reflect the average influenza seasons over time in order to aid long-term decision-making regarding the priority of influenza vaccinations. We presume that decision makers who use the results of the priority ranking will continue to adjust short-term strategies as information specific to each influenza season becomes available.

C. Literature Search and Abstraction

C1. Effectiveness Literature:

In total, we identified 27 articles on the effectiveness of influenza vaccinations in preventing influenza-associated mortality and influenza-like illness.³⁻²⁹ We first performed a Level I search³⁰ for data on the burden of disease, quality of life, effectiveness, adherence, delivery rates, and cost-effectiveness. The Level I search for effectiveness identified only 2 articles on the effectiveness of the vaccination in preventing influenza-related mortality. All other articles identified in the search were about the effectiveness of the vaccine in preventing influenza illness and hospitalization. Our initial analysis indicates that effectiveness in reducing influenza-related mortality is an influential variable in both CPB and CE. Therefore we performed Level 2 and 3 searches³⁰ that identified three additional studies of the effectiveness of the vaccination in reducing influenza-related mortality.

We initially abstracted 26 articles that assessed the relationship between influenza vaccination and influenza-related mortality or incidence of influenza-like illness in adults.^{3;5-13;15-29;31} Two articles identified later were also abstracted.^{32;33}

C2. Cost-effectiveness Literature:

We identified 14 potential economic evaluations of influenza vaccine in adults^{7;19;20;31;34-43} and we abstracted three of these studies.^{19;20;39} The reasons for excluding effectiveness and cost-effectiveness articles both before and after abstraction are provided in Sections D.3 and E.1 below.

C3. Vaccination Rates, Antigenic Match and Adherence Literature:

We extended our searches to Levels 2 and 3 to identify additional data on vaccination rates, antigenic match of each year's vaccine, and adherence to offers of influenza vaccinations. In total we identified 1,562 articles. As described below, 56 of these articles either provided data for our estimates, informed the structure of our model, or were evaluated for use in our model.

D. Clinically Preventable Burden (CPB) Estimate

Table 1 shows the summary calculations for CPB. Most of the data points in Table 1 are either estimates from the literature or are calculated from other data in the table. For data points taken from the literature, the “Data Source” column in Table 1 shows the reference numbers on which the estimate is based. For data points that are calculated within the table, the “Data Source” column shows the calculation formula. The letters in the formula refer to the row labels (left-most column of Table 1) for the data points from which the calculation is made. The “Base Case” column shows either the point estimate for each variable used in our calculation of CPB or the result of a calculation. The “Range” column shows the range over which the point estimates were varied in our sensitivity analysis. We created additional tables (not shown) to summarize the evidence and perform supporting calculations. In the following text, we describe relevant content from these tables.

D1. Burden of Influenza:

D1.1 Influenza-Associated Mortality:

Influenza-associated Mortality Rates: Rows c and d.

There would be 84,447 influenza-related deaths after the age of 50 in a US birth cohort of 4,000,000 individuals (row e, Table 1), given current immunization rates, current influenza mortality rates (rows c and d)⁴⁴ and the number of years of life lived after age 50 given current life-expectancy (rows a and b).⁴⁵ Estimates of the deaths attributable to influenza are uncertain due to inherent difficulties in measuring influenza’s role as a contributing factor in deaths with other associated conditions such as respiratory diseases or cardiovascular disease.^{24;44;46;47} Our estimate is based upon the influenza-associated mortality for all underlying causes of death as reported by Thompson et al. for persons 50 or more years old.⁴⁴ Mortality measures that are more narrowly defined were available, such as influenza-associated deaths with underlying pneumonia and influenza. However, influenza-associated mortality with all underlying causes was most consistent with the available estimates of the effectiveness of the vaccine in preventing mortality. Therefore, the incidence of influenza mortality with all underlying causes produces the most accurate estimate of CPB possible, given the available effectiveness data.³⁰ In sensitivity analysis, our lower bound is the incidence rate of influenza-associated illness with underlying causes of death from respiratory and circulatory deaths, and our higher bound is the incidence rate of all underlying causes, including deaths associated with both influenza and respiratory syncytial virus.⁴⁴ Our base-case estimate of the total number of deaths is higher than the total reported by Thompson et al.⁴⁴ for this age group (51,203) because their estimate largely reflected pre-baby boom birth cohorts of less than 4,000,000.

Influenza-associated Mortality in the Absence of Vaccinations: Rows e-k.

The mortality based on observed incidence rates (row e) is reduced by delivery of the vaccine, in order to adjust this estimate to reflect mortality in the absence of the vaccine. The adjustment formulas are shown in the source column for rows i and j in Table 1, the general form and derivation of which are described in the methods technical report.³⁰ National delivery rates for influenza vaccination are available from both the National Health Interview Survey (NHIS) and the Behavioral Risk Factor Surveillance System (BRFSS) for this calculation. Our mortality estimates are based upon observations from the 1990s. During this time, the BRFSS included questions on influenza vaccination status in 1993, 1995, 1997, and 1999. The median vaccination rate among US States ranged from 50.8% to 67.4% (average = 60.1%), with a slow upward trend over time.^{48;49} Responses to a similar question in the NHIS indicate an average vaccination rate

of 64.1% over years for which survey questions on vaccination were included (1991, 1993, 1995, 1997-1999).^{48;50;51} We use the average from NHIS because these data cover the entire decade and the NHIS provides data on delivery rates in the 50-64 year old age group during the mid to late 1990s. The average vaccination rate for ages 50-64 over 1995, 1997-1999 is 34.2%, with no pronounced time trend. We used the delivery rate of each age group to adjust the age-group specific mortality rates (rows i and j). Our estimate of the efficacy of the vaccine that is used in this adjustment is discussed below.

D1.2 Influenza-like Illness: Rows l and m.

We were unable to derive a CPB estimate based upon culture-proven cases because there are too few generalizable data on both incidence and corresponding effectiveness of the vaccine in reducing culture-proven cases. We use observed incidence rates of influenza-like illness among unvaccinated individuals to approximate the incidence in the absence of the vaccine. We recorded 11 estimates of the incidence of influenza-like illness in adults younger than age 70 from three of the studies that we abstracted for vaccine effectiveness data^{7;9;23} and from one additional study of zanamivir.⁵² Some of the studies included a small portion of children, and most study populations were dominated by working-aged adults. We found only one study providing reasonably generalizable estimates of the rate of influenza-like illness among older adults.¹³ We excluded incidence estimates among unvaccinated populations that were based on non-generalizable populations from nursing homes^{8;17;26;27;53} and estimates measured as culture-proven cases of influenza.^{7;9;13;27}

The included estimates were too few to determine whether incidence rates were different for younger and older adults. Therefore we combined the estimates of the 5 included studies.^{7;9;13;23;52} The included studies used different measures of influenza illness. They included influenza-like illness, febrile illness, upper respiratory tract illness, and febrile upper-respiratory tract illness. The included studies covered influenza seasons of 1987-1988, 1988-1989, 1989-1990, 1992-1993, 1997-1998, and 1998-1999. In order to estimate the incidence in an average-risk year, we calculate an estimate for each year, and then estimate the mean and median incidence across years. Estimates for each year reflect the average estimate for all studies that included that particular year. If a study reported estimates for multiple definitions of influenza-like illness, the estimates were averaged to create a single estimate for the study for each included year. Calculated in this way, the mean annual incidence over these 6 influenza seasons is 0.1511 (row l).

D1.3. Influenza-associated Hospitalizations: Rows n-q.

We count hospitalizations associated with influenza separately from other cases of influenza-like illness because the quality-of-life consequences of such illnesses are likely to be greater. Three studies provided hospitalization rates for influenza or pneumonia for individuals 65 years of age or older who had not received the influenza vaccine.^{22;24;25} The studies provided data on populations served by 3 managed care plans in the Midwest, Northeast, and Northwest over 10 influenza seasons: 1990-1991 through 1999-2000. We excluded estimates among unvaccinated populations who were residents of nursing homes^{26;27} and estimates from earlier publications of populations and influenza seasons.^{20;21} Among the included estimates, the mean annual incidence of hospitalizations across the included influenza seasons is 0.0090 (row p).

We were unable to identify appropriate estimates of influenza and pneumonia hospitalizations for unvaccinated persons 50-64 years of age. A recent national estimate of

influenza-associated hospitalizations⁵⁴ reports only a restrictive measure of influenza-associated hospitalization by age group. This measure was not compatible with the available data on effectiveness of the vaccine in preventing hospitalizations and therefore not appropriate for our calculation of CPB. Using this more restrictive definition, there are between 0.3 and 0.5 influenza-associated hospitalizations per 1,000 adults aged 50-64 years. A cost-effectiveness study of working adults aged 18-64 using a less restrictive case definition observed only one hospitalization for influenza-like illness or upper respiratory tract infections among more than 1,000 individuals over the 1997-1998 and 1998-1999 influenza seasons.⁷ Lacking other data, we use an estimate of 1 hospitalization per 1,000 among unvaccinated individuals age 50-64 (row n). Our sensitivity analysis shows that with an incidence this low (roughly one 10th the rate in older individuals) the estimate has negligible impact on CPB.

D.2 Adherence: Row r.

The primary distinction we make between efficacy and effectiveness is that effectiveness reflects the level of patient adherence that can be expected in every-day practice, while efficacy reflects 100% patient adherence.³⁰ Reasons for non-compliance with influenza vaccination include perceptions that the vaccine is not effective, individual perception of non-susceptibility to influenza and severe complications, and belief that the influenza vaccine causes infections, important adverse reactions, or interferes with medications.⁵⁵⁻⁶⁰ Estimates of adherence to clinician recommendations to be vaccinated are scarce. The best estimate of adherence to clinician offers of influenza vaccination is from an Ohio study of three interventions aimed at increasing provider adherence to immunization guidelines.⁶¹ This study reported the proportion of patients 65 or more years of age who were offered and accepted influenza vaccinations. Averaged across the three study arms, 85.6% of patients who were offered the vaccination were vaccinated. This estimate was similar to the vaccination rates achieved by reminder letters and postcards sent to older adults in 3 European studies identified during our Level 1 search.^{59;60;62} We use an estimate of 85% of adherence to offers from primary care clinicians to older adults to be vaccinated against influenza.

D.3 Vaccine Efficacy:

Twenty-seven studies were identified that examined the association between influenza vaccination status and incidence of disease, mortality, or utilization of health services.³⁻²⁹ Two studies were subsequently identified^{32;33} in a recent systematic review.⁶³ Nine were either excluded prior to abstraction or were marked with 'fatal flaws' by the reviewers as not appropriate for use in estimating CPB.³⁰ Reasons for exclusion included having updated results in a later included report about the same population,^{20;21} lack of a no-vaccination comparison group,^{14;28} study populations receiving amandatine,⁴ or studies that had two or more of the following limitations: no vaccination until after an outbreak started, non-generalizable study population, questionable retrospective ascertainment of vaccination status, and small sample size.^{8;11;18;29} One study was excluded after abstraction because the small study population combined with use of an early form of the vaccine made the estimates of the effect size substantially less reliable than other studies,¹⁶ and a second was excluded after abstraction because the reported outcome was all-cause mortality rather than influenza-associated mortality and because it did not report other outcomes used in our analysis.¹⁵ The studies on which our estimates of effectiveness were based included five RCTs,^{7;9;13;23;32} five case-control studies^{3;5;10;12;19} and eight observational studies.^{6;17;22;24-27;33}

D3.1 Efficacy in Preventing Mortality: Rows

Five studies provided estimates of the effectiveness of vaccinations in preventing mortality among adults.^{3;10;19;22;26} These studies were from three different countries (UK,³ Canada,¹⁰ and the U.S.^{19;22;26}) and between them cover all influenza seasons between 1980-1981 and 1995-1996. Four of the studies defined death as any death due to any cause among individuals with influenza,²⁶ influenza and pneumonia hospitalization,^{19;22} or any respiratory disease.¹⁰ The fifth study defined death as any death with influenza listed as the primary or secondary cause.³ As we did for our incidence estimates, we create an average estimate for each included influenza season and used the average across seasons in our calculations (42.9%, rows h and s in Table 1). Two studies^{19;22} had more influence in this estimate because each study covered a larger number of influenza seasons.

D3.2 Efficacy in Preventing Influenza-like Illness: Rows u

Nine studies^{7;9;13;17;23;26;27;32;33} provided estimates of the efficacy of influenza vaccinations in reducing the incidence of influenza-like illness. Variation in definitions of illness, age of study populations, vaccine matches, flu-seasons, and study design make it impossible to discern any association between the magnitude of efficacy estimate and any of these study characteristics. A recent meta-analysis of the vaccine among younger adults showed some of these factors to significantly impact effect size in randomized-controlled trials with clinically- or lab-confirmed influenza as the measured outcome.⁶⁴ The mean effectiveness in reducing influenza-like illness across the included influenza seasons (calculated as described above) is 18.9%.

D3.3 Efficacy in Preventing Hospitalizations: Row w

Nine studies^{5;6;10;12;19;22;24-26} contributed estimates of the effectiveness of influenza vaccinations in reducing hospitalizations for pneumonia or influenza, using various diagnosis codes and including a wide range of flu seasons during the 1980s and 1990s. The vast majority of the study populations were 65 years or older. Calculated across the included influenza seasons, the mean efficacy of the vaccine in reducing hospitalizations for influenza and pneumonia is 36.6%.

D.4 Effectiveness: Rows t, v, and x.

Our estimate of effectiveness of offering the vaccine in preventing each type of outcome (rows t, v, and x) is calculated as adherence multiplied by the respective efficacy estimate.

D.5. QALYs Saved (CPB Calculation).

D.5.1 QALYs Saved Through Prevented Mortality: Rows y-bb.

There are no direct observations of the extent of life expectancy (LE) gains from vaccination. Study subjects are typically not observed beyond a single influenza season, and therefore the number of years of additional life gained for each death that is prevented during the influenza season is not known. For most other conditions analyzed in the Prevention Priorities study, we use the life expectancy at age of death to estimate the years of life that would have been gained if the death had been prevented. However, individuals who are most at risk for influenza-associated mortality have underlying conditions that otherwise put them at greater risk for reduced life expectancy. Although comorbidities are an issue when calculating life-expectancy gains for most conditions, the potential to overstate life-expectancy gains using this

method is larger for influenza because the mortality component of our CPB estimate is based upon mortality from all causes that happened to be concurrent with an influenza infection. Therefore, we first calculate the average life expectancy (LE) at death using the weighted average of LE in 5-year age groups from life-tables⁴⁵ and the age at death for conditions with the ICD-9 codes⁶⁵ used by Thompson et al. for “underlying respiratory and circulatory deaths”.⁴⁴ We then use 75% of this estimate as our base-case estimate for life expectancy gains (= 16.4 years for the 50-64 year age group, and 5.6 years for the over 64 year age group), and we use 50% and 100% of this estimate as our lower and upper bounds in sensitivity analysis. No data are available to indicate how large the overstatement of years life lost would have been if we use 100% of the LE at age of premature death. 75% was chosen as an adjustment to LE that we felt was likely to improve the estimate without risking the mistake of a large arbitrary over-adjustment.

Total years of life saved (row bb) are calculated by multiplying the years gained per mortality prevented by the estimated number of influenza-associated mortalities prevented.

D.5.2 QALYs Saved Through Prevented Influenza-like Illness: Rows cc-gg.

Calculations of QALYs attributable to non-fatal cases require estimates of the duration of illness and the reduction in quality of life for each case. Nichol et al.²³ reported an average of 9.2 days of influenza-like illness per case among working-aged adults who have not been vaccinated. However, quality of life is unlikely to be substantially reduced over all of these days. Therefore, we approximate the average quality of life reduction from non-hospitalized cases by using our standard quality of life reduction of 0.30 for acute conditions³⁰ and an average duration of illness of 7 days per case.

D.5.3 QALYs Saved Through Prevented Hospitalizations: Rows hh-ll.

For hospitalizations, we assign an average duration of twice the duration of non-hospitalized cases (row ii), and we use the same quality of life reduction for acute conditions.

D.5.4 Total QALYs Saved.

Multiplying these estimates as shown in the source column of Table 1 yields 257,572 QALYs saved from prevented deaths (row bb), 15,223 QALYs saved from prevented illness (row gg), and 2,086 QALYs saved from prevented hospitalizations (row ll). Summed, these estimates provide our base-case CPB estimate of 274,881 QALYs saved over the lifetime of a birth cohort of 4,000,000 individuals.

D.6 Sensitivity Analysis for CPB

In single-variable sensitivity analysis, CPB is most sensitive to the variables related to the calculation of years of life saved: mortality rates (rows c & d), vaccine efficacy in preventing mortality (rows h & s), and average life-expectancy gained per death prevented (rows z and aa). CPB is also somewhat sensitive to adherence (row r). Simultaneously changing the three variables related to years-of-life-saved in the same direction produces our multivariate sensitivity analysis range of 90,800 to 639,000 QALYs saved.

E. Cost-Effectiveness (CE) Estimate

E.1 Cost-Effectiveness Literature.

We identified 14 economic evaluations of the influenza vaccine in adults^{7;19;20;31;34-43} and we abstracted three of these studies.^{19;20;39} The others were excluded prior to abstraction because:

1. they were based on evaluations outside the U.S. health care system^{34;38}
2. they evaluated the vaccination only in younger adults^{7;35}
3. they analyzed a limited age range among older adults^{31;40}
4. they provided scenario analysis without a well-defined base-case analysis of CE in the target age group^{36;37}
5. the results indicated net positive costs and the health outcomes in the study excluded mortality (therefore not producing a useful cost-effectiveness ratio for our purposes)⁷, or
6. they were updates^{41;42} of an abstracted version with more detailed cost-effectiveness reporting.²⁰
7. they were published prior to 1990, and examined influenza seasons in the 1970s.⁴³

Two of the abstracted studies showed a net savings. One estimated a savings of \$2.50 per person vaccinated (after adjustment to year 2000 dollars) based upon observations of persons 65 or more years of age over 10 years in a Washington state managed care organization.¹⁹ The other estimated a savings of \$182 per person vaccinated (averaged across study years and adjusted to year 2000 dollars) based upon observations of persons 65 or more years of age over 3 years in a Minnesota managed care organization.²⁰ Neither study summarized health benefits using QALYs. The third abstracted study estimated a CE ratio of \$232/QALY saved (after adjustment to year 2000 dollars) based upon the experience of the Medicare influenza demonstration project in 10 U.S. states.³⁹

Although none of the studies had ‘fatal flaws’ by either reviewer, each had several significant limitations for our purposes. The two studies which showed small cost-savings did not provide estimates of the QALYs which are needed to perform sensitivity analysis when changes in variables cause net costs to rise above zero. The one study which expressed results in terms of dollars per QALY reported too little detail to fully evaluate the adequacy of the estimate or to perform sensitivity analysis using our method for published studies.⁶⁶ Among the other important limitations, each study used cost data that were at least 10 years old, causing potentially large errors when adjusting results to year 2000 dollars; none of the studies included adults aged 50-64 years of age; two of the studies^{20;39} used seemingly very low vaccination costs (\$3.90 and \$5.90 after adjustment to year 2000 dollars); and one study included only cost savings of hospitalization for influenza.²⁰

E.2 Cost-Effectiveness Estimate Approach.

We produced our own CE estimate based upon our CPB estimate in order to provide a clear, updated estimate of CE that included individuals at ages 50-64; to obtain an estimate that is methodologically comparable to the CE estimates of other services evaluated in this study; and to provide full sensitivity analysis.

We present our estimate in Table 2. Table 2 has the same format as Table 1. We continue our lettering for row labels from Table 1 because the CE estimate is built upon 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.

One of the CE studies reviewed for this report (but not abstracted) provided detailed reporting of model design and results, including on-line appendices.³⁷ This study produced results for various attack rates. Among the attack rates analyzed in the CE study, the 20% attack rate was closest to our estimate of the average annual incidence of influenza-like illness (.1511,

row l of Table 1). In addition, the mortality and hospitalization incidence rates underlying the number of deaths and hospitalizations in our CPB estimate are consistent with those estimated by the authors for a 20% attack rate (see figure page 665 of Meltzer et al.). For our CE estimate, we used Meltzer's study as the source for all variables not included in our CPB estimate. We incorporated the study's age group-specific influenza costs (inflation adjusted to year 2000 dollars). We applied the study's estimates of cost-per-case for people 20 to 64 year of age to the narrower age group of 50-64 in our estimate.

A complete birth cohort approach typically requires year-by-year modeling and discounting of future benefits back to a single base-year; typically this is the first year the preventive service is offered to the birth cohort (in this case, age 50). Because all costs and benefits from the vaccine are seen in one year, we need only to discount the future years of life saved from a death prevented during the vaccination season back to the present value in the year in which the death is presented. We could further discount years of life saved, all costs, and all quality-of-life improvements back to the first year the preventive service is offered to the birth cohort. However, the effect of doing so would be proportional to the numerator and denominator of the CE ratio because all benefits from future years of life gained accrue in the same year that the costs of administering the vaccine accrue, so the CE ratio itself would not change.

E.3 Cost-Savings from Vaccinations: Rows nn-uu.

The per-case cost estimates for treating influenza from Meltzer et al., after inflation adjustment, are shown separately for cases treated in the hospital (inclusive of the individual's outpatient costs) (rows nn and oo), and cases treated only in the outpatient setting (row ss). We use a simple average of the Meltzer et al's age group-specific outpatient costs because the difference in outpatient costs by age group from Meltzer et al. were negligible and our model predicts roughly equal numbers of cases in the two age groups (50-64 and 65+). We apply these estimates to an annualized estimate of our incidence rate and hospitalization rates from our CPB calculations. We adopted Meltzer et al's estimate that 47% of non-hospitalized cases received outpatient care in all age groups (row qq). In order to maintain consistency across preventive services analyzed in this project, we did not incorporate the indirect costs of influenza cases used by Meltzer et al.

E.4 Vaccination Costs: Rows vv-ww.

The one other exception to the use of the cost estimates of Meltzer et al. was the cost of vaccination, to which the estimate of CE was particularly sensitive. Our estimate of the health sector cost of vaccination (row vv, Table 2) is the average of 4 estimates of private-sector costs adjusted to year 2000 dollars,^{7;19;20;37} including the midpoint of the range used by Meltzer et al.³⁷ To improve consistency across the preventive services included in our study, we used our standard method of valuing time for patients to travel to the clinic and receive the service. We assume that it takes 2 hours to receive the vaccination, but that only half of this time is attributable to the vaccination itself because some patients will receive one or more other services at the same time. We use average hourly earnings plus benefits in 2000⁶⁷ to estimate the value of patient time. The resulting estimate of the value of patient time is \$21.16 per person in year 2000 dollars per person vaccinated (row ww). This estimate is close to that used by Bridges et al.⁷ (\$14.70 in 1999 dollars) and within the range used by Meltzer et al. (\$8 to \$39 in 1995 dollars).³⁷ For sensitivity analysis, we change the value of time by 25% in both directions and

allowed the portion of the 2 hours time that is attributable to influenza vaccination to vary from 33% to 67%.

E.5 Discounting and CE Calculation: Rows yy-eee.

The average annual net cost of vaccination is \$1.49 billion in year 2000 dollars (row yy). We use present value tables developed for the Prevention Priorities project to estimate the average present value of years of life gained. At a 3% discount rate, the 16.4 years of life per death prevented for the 50-64 year age group, and the 5.6 years of life per death prevented for the over 64 year age group (rows z and aa) have a present value (in the year the death is prevented) of 5.85 years (row aaa). Applying the same quality of life estimates, duration of illness estimates, and vaccination efficacy and adherence as used for CPB, yields an average of 254,275 QALYs saved over the remaining years of a birth cohort when years of life are discounted as above (row ccc). Dividing net costs by QALYs saved yields a CE ratio of 5,858 dollars per QALY saved.

For purposes of comparison to the results of the three abstracted studies noted above,^{19;20;39} the exclusion of the costs for patient time to be vaccinated results in a net cost of - \$5.52 per person vaccinated (not shown in table).

E.6 Sensitivity Analysis for CE

The sensitivity analysis reported by the abstracted studies^{19;20;39} only indicated that the severity of the flu season (incidence rate) and the antigenic match of the vaccine may cause substantial variation in CE of the influenza vaccine from year to year. In our estimate of CE the most important variables are the cost of the vaccine, the value of patient time to receive the vaccine, and the efficacy of the vaccine in preventing hospitalizations. Secondly, the estimates of mortality incidence, efficacy of the vaccine in preventing mortality, the years of life gained per death prevented, incidence of hospitalization, and costs of hospitalizations are also influential variables. We explored combinations of these variables in multivariate sensitivity analyses to find the combination of three variables that produce the lowest and highest CE estimates.³⁰ Simultaneously changing the costs of the vaccine, the cost of patient time to receive the vaccine, and the efficacy of the vaccine in reducing hospitalizations produces our lower bound estimate of \$7.25 saved per person vaccinated. Simultaneously changing the cost of patient time to receive the vaccine, mortality incidence, and the years of life gained per death prevented produces a positive CE ratio of \$22,000 per QALY saved.

F. Scoring

We ranked services in the Prevention Priorities project based upon scores for CPB and CE rather than point estimates.^{30;68} For each measure, we assigned scores according to the quintile in which the service's CPB and CE estimates fall among all services included in the study scope. Thus, services having the highest CPB or best-cost-effectiveness received a score of 5.

The base-case estimate of 274,881 QALY saved with influenza vaccination resulted in a CPB score of 4. Two other services with CPB scores of 4 had higher point estimates and two had lower point estimates. The lowest estimate for the CPB of influenza from multivariate sensitivity analysis would result in a CPB score of 3 and the highest estimate would result in a CPB score of 5. Changes to any one variable by itself would not reduce the CPB score to a 3. However, changes to the efficacy of the influenza vaccine in preventing mortality would produce a score of 5 when moved to the most favorable estimate shown in Table 1.

The base-case CE ratio of \$5,900 per QALY saved was the lowest CE ratio (most cost-effective) among services receiving a CE score of 4. The most and least favorable estimates from multivariate sensitivity analysis (\$7 saved per person vaccinated and \$22,000/QALY saved) would result in CE scores of 5 and 3 respectively. In the case of the most favorable results, influenza vaccinations would have the least cost-savings among services with a CE score of 5. Changes to any one variable by itself would not result in CE scores of 3 or 5.

The base case estimates produced a total score of 8 for this service, and the multivariate sensitivity analysis indicated that total scores from 6 to 10 were possible. Overall, changes to any one variable in the less favorable direction failed to reduce the total score to either a 6 or 7, while changes to the efficacy of the influenza vaccine in preventing mortality, in a more favorable direction could produce a total score of 9 but not 10. Therefore, despite relatively high sensitivity of the base-case estimates to several uncertain variables, the total score for this service was relatively insensitive to any one variable by itself.

G. Limitations

Our simplified models provided transparent estimates of the benefits and CE of offering influenza vaccine to a birth cohort of 4,000,000 individuals starting at the age of 50. Like all models, the accuracy of our estimate was 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 vaccine in preventing mortality and hospitalizations, mortality incidence, and 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.

Our incidence rates for non-fatal cases were observed in non-vaccinated populations. These populations may have received partial protection from living in the community with vaccinated populations. Therefore, the use of these data may have caused us to understate influenza incidence in the absence of the vaccine. Likewise, efficacy estimates based on comparisons between those who did and did not receive the vaccine, but were living in the community with individuals who did receive the vaccine, may be biased. The potential for this bias varied somewhat from study to study.

The estimates of effectiveness against hospitalizations and deaths were based entirely on observational studies. If more frail individuals fail to receive the vaccine, then comparisons of those who did and did not receive the vaccine may cause the estimates of effectiveness against hospitalizations and death to be overstated.^{63;69} The potential impact of this bias was reduced by limiting hospitalizations to those for influenza and pneumonia, and limiting deaths to influenza-associated deaths. However this did not eliminate the potential for the estimated health impact and cost savings to be overstated by this bias.

Our estimate excluded adverse events from the influenza vaccine. Three randomized controlled trials have found no differences in systematic reactions (fever, fatigue, headaches, etc) between vaccination and placebo groups, but they found statistically significant differences in mild localized reactions (soreness at injection site, swelling, itching).⁷⁰⁻⁷² Severe arm soreness occurred in approximately 2% of vaccinated individuals.⁷¹ One or more other localized reactions occurred in about 20% of vaccinated individuals.⁷¹ Few individuals reported reductions in quality of life after vaccination,^{70;71} and there was no difference in this measure between cases and controls.⁷¹ We identified no data to quantify the duration and quality of life reduction of localized reactions other than the duration of arm soreness (less than 48 hours for 80% of

individuals with arm soreness).⁷¹ Given these data, it was reasonable to expect that localized reactions have a minor impact on quality of life when compared to the frequency, duration, and severity of non-fatal influenza illness prevented, and that the impact was quantitatively trivial relative to the number of QALYs saved through reduced mortality.

Other than reduced duration of illness from reduced hospitalizations, we have not included an estimate of improvement in quality of life from reduced severity of illness for individuals who were vaccinated but still get ill. In a study of working-aged adults, vaccinated study participants who had influenza-like illness averaged 1.3 days shorter duration of illness than unvaccinated participants.²³ There were no data on the relative severity of this marginal 1.3 days in unvaccinated participants, or data on whether other days of illness were less debilitating among vaccine recipients. To explore the potential impact of this exclusion, we estimated that if each of the 1.3 prevented days had the same quality of life reduction that we assigned to influenza illness (0.30) and there was no further improvement in quality of life for the other illness days, then about 15,000 additional QALYs could have been prevented by vaccinations than our CPB estimate indicates. If this estimate is accurate, it would increase our CPB estimate by 5% (from 274,881 QALYs).

We considered using broader definitions of influenza-related hospitalizations by adding estimates of respiratory illness and cardiovascular disease. However, we were unable to locate suitable estimates. The available incidence data of hospitalizations for these other conditions^{10;20-22} were based on any diagnosis code in the medical claims form rather than just the primary diagnosis. Therefore, they may include a substantial number of the influenza and pneumonia hospitalizations that were already included.

Table 1. Calculation of Clinically Preventable Burden of the Influenza Vaccine Being Offered to a Birth Cohort of 4,000,000 Starting at Age 50.

		Base Case Estimate	Source	Range for Sensitivity Analysis
Person-years in target population from birth cohort of 4,000,000				
a	Number of person-years between ages 50-64	53,357,760	45	
b	Number of person-years after age 64	58,699,920	45	
Influenza mortality after age 49 in birth cohort of 4,000,000				
c	Annual influenza-related mortality rate per 100,000 ages 50-64	12.5	44	+/- 25%
d	Annual influenza-related mortality rate per 100,000 ages 65+	132.5	44	+/- 25%
e	Total unadjusted influenza related deaths after ages 49	84,447	$= (axc + bxd) / 100,000$	
f	Vaccination rate in ages 50-64 in 1990s	34.2%	48;51	+/- 25%
g	Vaccination rate in for ages 65+ in 1990s	57.4%	48;50;51	+/- 25%
h	Efficacy of influenza vaccine in preventing influenza-related mortality	42.9%	3;10;19;22;26	35% to 55%
i	Predicted annual influenza mortality rate per 100,000 ages 50-64 in the absence of vaccinations	14.6	$= c / (1 - fxh)$	
j	Predicted annual mortality rate per 100,000 in the absence of vaccinations ages 65+	175.8	$= d / (1 - gxh)$	
k	Predicted influenza-related mortalities after age 49 in birth cohort	110,986	$= (axi + bxj) / 100,000$	
Influenza-like illness after age 49 in birth cohort of 4,000,000				
l	Annual incidence of influenza-like illness in unvaccinated individuals	0.1511	7;9;13;23;52	0.09 to 0.25
m	Influenza cases after age 49 in unvaccinated individuals	16,931,601	$= (a+b) \times l$	
Influenza-related hospitalizations after age 49 in birth cohort of 4,000,000				
n	Annual hospitalization rate for pneumonia or influenza ages 50-64 in unvaccinated individuals	0.0010	7;54	0.000 to 0.0020
o	Number of hospitalizations for pneumonia or influenza ages 50-64 in unvaccinated individuals	53,358	$= axn$	
p	Annual hospitalization rate for pneumonia or influenza after age 65+ in unvaccinated individuals	0.00900	22;24;25	.0085 to .0111
q	Number of hospitalizations for pneumonia or influenza after age 65+ in unvaccinated individuals	528,411	$= bxp$	
Vaccine effectiveness				
r	Adherence with vaccine	85.0%	61	75% to 95%
s	Efficacy of influenza vaccine in preventing influenza-related mortality	42.9%	3	
t	Effectiveness of offering vaccine in preventing mortality	36.5%	$= rxh$	
u	Efficacy of vaccine in preventing influenza-like illness	18.9%	7;9;13;17;23;26;27	10% to 30%
v	Effectiveness of offering vaccine in preventing influenza-like illness	16.1%	$= rxu$	
w	Efficacy of influenza vaccine in preventing hospitalizations for influenza and pneumonia	36.6%	5;6;10;12;19;22;24-26	25% to 50%
x	Effectiveness of offering vaccine in preventing hospitalizations for influenza and pneumonia, ages 50+	31.1%	$= rxw$	
QALYs Saved after age 49 through prevented mortality				
y	Predicted mortalities prevented	40,477	$= kxt$	
z	Average life expectancy at death ages 50-64	16.4	45;65	5.05 to 10.1
aa	Average life expectancy at death ages 65+	5.6	45;65	
bb	Years of life saved	257,572	$= ((axi)/100,000)$	

			$xz+(bxj/100,000) \times aa) \times t$	
	QALYs saved after age 49 through prevented influenza-like illness			
cc	Predicted non-hospitalized cases prevented	2,638,621	= mxv	
dd	Duration of illness in years (= 1 week)	0.0192	²³	0.5 to 2 weeks
ee	Year-equivalents of illness prevented by reduced non-hospitalized cases	50,743	= ccxdd	
ff	Quality of life reduction per year (QALY weight)	0.30	Study methods (see text)	0.20 to 0.40
gg	QALYs saved due to reduced non-hospitalized cases	15,223	= ee×ff	
	QALYs saved after age 49 through prevented hospitalizations			
hh	Predicted hospitalizations for pneumonia or influenza prevented	180,810	= (o+q)×x	
ii	Duration of illness in years (= 2 weeks)	0.0385	Assumed	1 to 3 weeks
jj	Year-equivalents of illness prevented by reduced hospitalized cases	6,954	= hh×ii	
kk	Quality of life reduction per year (QALY weight)	0.30	Study methods (see text)	0.20 to 0.40
ll	QALYs saved due to reduced hospitalized cases	2,086	= jj×kk	
mm	Total QALYs saved after age 49 in birth cohort of 4,000,000 (CPB)	274,881	=bb+gg+ll	

Table 2. Calculation of Cost Effectiveness of the Influenza Vaccine Being Offered to a Birth Cohort of 4,000,000 Starting at Age 50.

		Base Case Estimate	Source	Range for Sensitivity Analysis
Health care costs savings				
nn	Cost per hospitalized case, ages 50-64	\$ 7,276	³⁷	+/- 25%
oo	Cost per hospitalized case, ages 65+	\$ 8,278	³⁷	+/- 25%
pp	Total hospitalization case savings	\$ 1,480,166,157	= oxxxnn + qxxxoo	
qq	Percent of non-hospitalized cases receiving care	47%	³⁷	35% to 60%
rr	Number outpatient treated cases all ages	7,684,421	=(m-o-q) x qq	
ss	Cost per outpatient treated case all ages	\$ 198	³⁷	+/- 25%
tt	Outpatient care case savings	\$ 245,341,771	= rrxssxv	
uu	Total Savings	\$ 1,725,507,928	=pp+ tt	
Vaccination Costs				
vv	Per vaccination healthcare costs	\$ 12.59	^{7,19,20,37}	\$6 to \$18
ww	Per vaccination patient time and travel costs	\$ 21.16	⁶⁷	\$10.58 to \$35.27
xx	Lifetime vaccination costs	\$ 3,215,122,469	= (a+b)xr x(vv+ww)	
Cost Effectiveness				
yy	Net Costs	\$ 1,489,614,542	= xx - uu	
zz	Discount Rate	3%	see text	
aaa	Average present value of LY saved per death from year of immunization	5.85	see text	4.77 to 8.86
bbb	Discounted LY saved	236,966	= yxaaa	
ccc	Discounted QALYs saved	254,275	=bbb+gg+ll	
ddd	CE	\$ 5,858	=yy/ccc	
eee	Net costs per vaccination	\$ 15.64	=yy/((a+b)xr)	

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