Influenza Immunization for Adults 18 Years and Older

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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).

This report describes the methods, evidence, clinically preventable burden and cost effectiveness of offering influenza vaccine to a birth cohort of 4 million individuals. It builds on a prior report of the value of influenza immunization for ages 50 and older. In 2010, the Advisory Committee on Immunization Practices (ACIP) expanded its recommendation for annual seasonal influenza vaccination to include healthy adults aged 18 to 49. Our main results are for all ages combined, but results are also stratified by age groups reflecting changes in the ACIP recommendation over time (18-49 years, 50 to 64 years, 65 years and older). In a 2015 update, cost data were inflation-adjusted to 2012 dollars and an updated methodology for calculating vaccine-costs was applied across the services to improve comparability (see "Vaccination Costs" section in technical report for details).

A. ACIP Recommendation

The Advisory Committee on Immunization Practices (ACIP) in 2010 recommended annual seasonal influenza vaccinations for all persons aged six months and older.[1] The recommendation expanded seasonal influenza vaccination to include healthy adults aged 18 to 49 years. Previously, ACIP recommended vaccination for persons aged 50 years and older, health care personnel and other persons who were likely to transmit influenza to those at high risk, pregnant women, breastfeeding mothers and all persons who were in contact with infants or children younger than five years old, adults at high risk due to chronic conditions, and anyone who wanted to reduce the likelihood of influenza infection. [2]

In response to the 2010 ACIP recommendation, this evaluation focuses on vaccinations for the general population and estimates the benefits and cost-effectiveness of offering influenza vaccine to a birth cohort of four million individuals starting at age 18. Results are presented for four age groups: 18-49, 50-64, 65+, and 18+. Vaccination of children is analyzed separately. Vaccination of caregivers and groups at high risk is outside the scope of the Prevention Priorities project, which focuses on services for the general population.

Prior to 2010, ACIP recommendations for the use of Influenza A (H1N1) 2009 Monovalent Vaccine identified five target groups: pregnant women, persons who live with or care for infants younger than 6 months, health care and emergency medical services personnel, persons ages 6 months to 24 years, and persons ages 25 to 64 years who have medical conditions that put them at higher risk for influenza-related complications.[3] In addition, the ACIP recommended that, once vaccination programs were able to meet demand, vaccination should be expanded to all persons ages 25 to 64 years and then, once that demand was met, it should be offered to all persons ages 65 years or older. The H1N1 vaccine was recommended in response to a pandemic, in contrast to seasonal influenza. Because the epidemiology of pandemic influenza is different from that of seasonal influenza (i.e., different rates of attack, hospitalization, and death by age group), averaging the results from a pandemic period with that from seasonal experience would produce unstable estimates. Therefore, this analysis was limited to seasonal influenza vaccination.

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 clinically preventable burden (CPB) and cost effectiveness (CE) of influenza vaccinations may vary significantly over time. We aimed to create CPB and CE estimates that reflects the average of multiple influenza seasons over time to aid long-term decision-making regarding the priority of influenza vaccinations. To estimate vaccine effectiveness over time, we averaged the estimates for all studies from a particular year, and then estimated the average effectiveness across years. Similarly, we averaged incidence rates across years.

C. Outcomes

Our evaluation of the clinically preventable burden and cost-effectiveness of the seasonal influenza vaccination for adults ages 50 and older recognized three outcomes: influenza-like illness (ILI), influenza-associated hospitalization, and influenza-associated mortality. However, at the time of the literature search, we were unable to find studies that estimated the efficacy of influenza vaccine in preventing hospitalizations or mortality among adults ages 18-49. Three articles measured the effectiveness of influenza vaccinations in preventing influenza-associated hospitalizations[4-6], but two were excluded because the study populations were non-generalizable[5,6] and the third identified only one influenza-associated hospitalization among more than 1,000 subjects over the 1997-1998 and 1998-1999 influenza seasons[4]. Therefore, we did not estimate the impact of influenza vaccine on influenza-associated hospitalizations or mortality for adults aged 18-49. Compressed mortality data report less than one influenza-related death per million prior to age 50, and fewer than 50 deaths per million for influenza and pneumococcal combined.

D. Clinically Preventable Burden (CPB)

Table 1 shows the summary calculations for CPB for four age groups within a birth cohort of four million: Ages 18-49, Ages 50-64, Ages 65+, and Ages 18+. For each age group, we calculated the CPB from influenza immunization at each year of age within the age range. 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 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. We created additional tables (not shown) to summarize the evidence and perform supporting calculations. In the following text, we describe relevant content from those tables.

D1. Burden of Influenza

Incidence of Influenza-like Illness (ILI) in the Absence of Vaccinations

We used observed incidence rates of influenza-like illness and paired this with estimates of vaccine effectiveness in reducing influenza-like illness to estimate the health impact and cost-effectiveness of vaccination. We were unable to derive a CPB estimate based on culture-proven cases because there were too few generalizable data on the incidence of culture-proven cases across multiple influenza seasons.

We used estimates of influenza-like illness among unvaccinated individuals in randomized and observational studies to approximate the incidence of infection in the absence of the vaccination. We recorded 35 estimates of the incidence of influenza-like illness in adults from 11 studies.[4,8-17] One of the studies included a small portion of children,[10] three studies were of populations over age 60 or 65,[8,11,16] but most studies were of working-age adult populations. The included estimates were too few to determine whether incidence rates were different for younger and older adults. Therefore, we combined estimates over all ages.

These studies used somewhat different definitions of ILI, but they were consistently defined as illness with fever and systemic symptoms. The included studies covered the influenza seasons of 1967-68, 1983-1984 through 1989-1990, 1991-1992, 1997-1998 through 1999-2000, and 2001-2002 through 2005-2006. To estimate the incidence in an average-risk year, we calculated an estimate for each year and then estimated the mean 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 ILI, the estimates were averaged to create a single estimate for the study for each included year. Because our goal was to represent all influenza seasons equally, our yearly and overall averages were not weighted by study sample size. However, consistent with our estimate of vaccine effectiveness, we excluded small studies because we found potential publication bias as described below. Excluding studies with sample sizes of fewer than 500 persons and calculating as described above, the mean annual incidence during these 17 influenza seasons was 0.149 (Table 1, row b). Table 3 summarizes the sources and estimates used for the incidence of ILI. There would be 36.2 million cases of influenza-like illness over the adult years of a birth cohort of 4 million unvaccinated individuals (Table 1, row c).

Incidence of Influenza-associated Hospitalizations in the Absence of Vaccinations

We count hospitalizations associated with influenza separately from other cases of ILI because the quality-of-life consequences of such illnesses are likely to be greater. Because evidence of seasonal influenza vaccine effectiveness in preventing hospitalizations was lacking for younger adults, influenza-associated hospitalization was not included for ages 18-49. Two studies provided hospitalization rates for influenza or pneumonia for individuals 65 years or older who had not received influenza vaccine.[18,19] Both studies provided data on populations served by managed care plans: one in the Midwest, Northeast, and Northwest over 10 influenza seasons, 1990-1991 through 1999-2000; the other in Hawaii over three influenza seasons, 1994-1995 through 1996-1997. We excluded estimates from studies when updated estimates on the same population were available from a later study[20-24] and when the unvaccinated populations were residents of nursing homes.[25,26] The estimate of annual incidence of hospitalizations across the included influenza seasons is 0.0072 in adults age 65 and older (row d).

We were unable to identify appropriate estimates of influenza and pneumonia hospitalizations for unvaccinated persons 50 to 64 years old. A recent national estimate of influenza-associated hospitalizations[27] reported only a restrictive measure of influenza-associated hospitalization by age group. This measure was not compatible with available data on effectiveness of the vaccine in preventing hospitalizations and, therefore, not applicable to our calculation of CPB. Using this more restrictive definition, there are 0.3 to 0.5 influenza-associated hospitalizations per 1,000 adults 50 to 64 years old. A cost-effectiveness study of working adults 18 to 64 years old using a less restrictive case definition observed only one hospitalization for ILI or upper respiratory tract infections among more than 1,000 individuals over the 1997-1998 and 1998-1999 influenza seasons.[4] Lacking other data, we use an estimate of one hospitalization per 1,000 among unvaccinated individuals 50 to 64 years old (row e).

Incidence of Influenza-Associated Mortality

Because evidence of seasonal influenza vaccine effectiveness was lacking for younger adults, influenza-associated mortality was not included for ages 18-49. There would be 92,270 influenza-related deaths in persons older than age 50 in a U.S. birth cohort of 4 million individuals (Table 1, row g), given current immunization rates, current influenza mortality rates,[28] and the number of years of life lived after age 50 given current life expectancy.[29] Estimates of deaths attributable to influenza are uncertain due to inherent difficulties in measuring influenza's role as a contributing factor in deaths with associated conditions (e.g., respiratory or cardiovascular disease).[23,28,30,31] Our estimate is based on influenza-associated mortality for all underlying causes of death reported by Thompson et al. for persons 50 years or older.[28] More narrowly defined mortality measures, such as influenza-associated deaths with underlying pneumonia and influenza, were available. 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.[32] 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.[28] Our base-case estimate of the total number of deaths is higher than the total reported by Thompson et al.[28] for this age-group (51,203) because their estimate largely reflected pre-Baby Boom birth cohorts of fewer than 4 million.

Influenza-associated Mortality in the Absence of Vaccinations

Our estimate of mortality burden due to influenza (row g) was based on influenza-associated mortality rates published by Thompson et al. for the 1990-1991 through 1998-1999 influenza seasons. Those mortality rates incorporated the effects of vaccine use during the time for which the rates were estimated (i.e., influenza-associated mortality rates would have been higher if vaccines were not in use). Therefore, we used vaccination delivery rates from the same period as the observed mortality rates, the 1990s, to estimate influenza-associated mortality in the absence of vaccine use. The adjustment formulas are shown in the source column for rows j and k in Table 1, the general form and derivation of which are described in the methods report.[32] 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 on observations from the 1990s. During this time, the BRFSS included questions on influenza vaccination status in 1993, 1995, 1997, and 1999 for respondents ages 65 or older. The median vaccination rate for persons ages 65 or older among US States ranged from 50.8% to 67.4% (average = 61.1%), with a slow upward trend over time.[33,34] A similar question was included in the NHIS over years for which survey questions on vaccination were included.[33,35,36] We use the average from NHIS because these data cover the entire decade, and the NHIS provides data on delivery rates in the 50- to 64-year-old age-group during the mid to late 1990s. The average vaccination rate for persons ages 65 or older during 1991, 1993, 1995, and 1997 to 1999 was 57.4%. The average vaccination rate for persons ages 50 to 64 years during 1995 and 1997 to 1999 was 34.2%, with no pronounced time trend. We used the delivery rate of each age-group to adjust the age-group–specific mortality rates. Our estimate of the efficacy of the vaccine used in this adjustment is discussed below.

D2. Adherence

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.[32]

Reasons for non-adherence with influenza vaccination recommendations include perceptions that the vaccine is not effective, perception of non-susceptibility to influenza and severe complications, and belief that the influenza vaccine causes infections, important adverse reactions, or interferes with medications.[37-42] Estimates of adherence to clinician recommendations to be vaccinated are scarce. Among older adults, 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.[43] This study reported the proportion of patients 65 years or older 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 three European studies identified during our Level 1 search.[41,42,44] We use an estimate of 85% of adherence to offers from primary care clinicians to older adults to be vaccinated against influenza (Table 1, row l).

Healthy adults aged 18-49 had not been among the groups recommended for seasonal influenza vaccination until 2010, and vaccination rates among this age group prior to the ACIP recommendation had been low. Influenza vaccination rate estimates for adults aged 18-49 from the National Health Interview Survey for years 2000-2006 range from 10% to 18%; the estimate for the three quarters ending September, 2007 was 17.6%.[45] A RAND Corporation national survey found that 20.9% of adults not specifically recommended for the vaccine had received the seasonal influenza vaccine during the 2009-2010 season.[46] An estimate of the percentage of adults aged 18-49 who would receive the seasonal influenza vaccine if it were offered by their primary care clinician is wanting. A study of opt-out vs. opt-in work-site invitation for influenza vaccination found that 45% of university faculty and staff received vaccination when offered under the opt-out condition.[47] That study was before the ACIP's universal recommendation: subjects in the study were not exposed to a face-to-face offer with a clinician. Adherence to a vaccination offer in a clinician's office would likely generate greater adherence than a work-site offer, and thus, lacking additional evidence of adherence, we used an estimate of 60% of adherence for adults aged 18-49 to be vaccinated against influenza, a rate greater than the worksite study but less than our rate of 85% for adults ages 50+.

D3. Vaccine Efficacy

We conducted structured literature reviews at two time points. We conducted a literature search and abstraction focused on ages 50 and older in 2006. We updated the literature search to include any more recent articles and articles for younger adults in 2010. We performed a Level 1 search[32] for effectiveness on all outcomes, and expanded our literature search to Levels 2 and 3 for effectiveness in preventing mortality due to the sensitivity of results with respect to this model variable. The searches included identification of articles in Pubmed, articles cited in a published review, [48] and additional articles cited in the articles from the first two search methods of manuscript identification. We included

both randomized control trials and observational studies to increase the number of influenza seasons represented in our estimates.

Combined across the two literature reviews, we identified 66 articles on the effectiveness of influenza vaccinations in preventing influenza-associated mortality and influenza-like illness.[4-6,8-26,49-92] Articles about effectiveness studies were not selected for abstraction if the study outcome was culture-confirmed influenza and no other outcome was reported. This is because too few studies with limited generalizability provided estimates of the incidence of culture-confirmed cases to provide a basis for estimating burden of disease and health impact across a representative sample of influenza seasons. If an effectiveness article reported multiple outcomes, including culture-confirmed influenza, the article was selected and abstracted, but the results associated with the culture-confirmed outcome were not used.

Forty-six studies were either excluded prior to abstraction, were marked with "fatal flaws" by the reviewers as not appropriate for use in estimating CPB, or were excluded based on small sample size to prevent deriving a biased estimate of effectiveness due to publication bias. Reasons for exclusion included: lack of a no-vaccination comparison group;[56,61] study population received the antiviral drug amantadine;[51] study outcome measures were not applicable to our model, such as hospitalization for any respiratory disease or all-cause mortality,[67,68,70,90-92] non-generalizable study population, or[5,6,62,80-83] experimental vaccine intervention;[5,6,84] reviewers were unable to verify reliability of study methods, data, or outcome measure;[85-89] or studies that had two or more of the following limitations which combined reduced reviewer confidence in the estimate of effect size: no vaccination until after an outbreak had begun, limited generalizability of study population, questionable retrospective ascertainment of vaccination status or illness, or small sample size.[25,26,54,57-59,63-65,69] We also excluded estimates from studies when updated estimates on the same population were available from a later report.[20-24,71,78,79] Finally, six additional studies that reported effectiveness against ILI were later excluded to reduce the risk of deriving an effectiveness estimate that reflects publication bias.[72-77] Studies with fewer than 500 subjects had an average vaccine effectiveness of 51%, and all but one of them reported vaccine effectiveness of 30% or more; none of the effectiveness estimates were less than zero. In contrast, the estimates from larger studies averaged 23%, and five were less than zero. Therefore, we excluded studies with sample sizes of less than 500.

After these exclusions, the studies on which our estimates of effectiveness were based included nine randomized controlled trials,[4,8-11,13,14,16,17] five case-control studies,[49,50,53,55,60] and six observational cohort studies.[12,15,18,19,52,66] The included studies covered the influenza seasons of 1967-68, 1985-1986 through 1989-1990, 1991-1992, 1997-1998 through 1999-2000, and 2002-2003 through 2005-2006. To estimate the vaccine effectiveness in an average-risk year, we calculated an estimate for each year and then estimated the mean effectiveness 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. Because our goal was to represent all influenza seasons equally, our yearly and overall averages were not weighted by study sample size.

ACIP recommended both live, attenuated influenza vaccine (LAIV) and inactivated influenza vaccine (TIV) for persons aged 2-49 years not at high risk for complications of influenza.[1] Comparative studies of LAIV and TIV efficacy had been inconclusive at the time of the literature search and therefore we combined effectiveness measures for both LAIV and TIV in our overall vaccine effectiveness measure. A 1994 study comparing the efficacy of cold-adapted and inactivated influenza A vaccines[10] and a small 2000 study that evaluated the efficacy of cold-adapted and inactivated vaccines after challenging subjects with wild-type influenza[93] found both vaccines to be efficacious, with no significant difference between the vaccines. A multiyear study comparing the effectiveness of inactivated and live attenuated vaccines against culture-confirmed influenza has reported inconclusive results over three influenza seasons.[94-96] Finally, a comparison of inactivated and live attenuated vaccines among a military population found the inactivated vaccine to offer slightly greater protection among non-recruits, while the live attenuated vaccine was significantly more protective among recruits.[97]

Table 3 summarizes the sources and estimates used for vaccine efficacy and they are described below by outcome (influenza-like illness, hospitalizations for influenza and pneumococcal disease, and deaths among individuals hospitalized for influenza or pneumococcal disease).

Efficacy in Preventing Influenza-like Illness

The 12 studies on which our estimate of the efficacy of influenza vaccinations in reducing the incidence of influenza-like illness were based included 10 randomized controlled trials[4,8-11,13,14,16,17,71] and two observational studies.[12,15] As with the studies used to estimate incidence of influenza-like illness, one of the studies included a small portion of children,[10] three studies were of populations over age 60 or 65,[8,11,16] but most studies were of working-age adult populations. Vaccine efficacy estimates by age of study population are shown in Figure 1. The included estimates were too few to determine whether vaccine effectiveness differs for younger and older adults. Therefore, we combined estimates over all ages. Additional variation in study populations, vaccine matches, flu seasons, and study design make it difficult to discern association between the magnitude of efficacy estimate and any one of these study characteristics. However, a 2004 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.[98] The mean efficacy in reducing influenza-like illness across the included influenza seasons is 23.6%, when calculated to provide equal weighting for each represented influenza season as described above for the calculation of the ILI incidence (Table 1, row m).

Efficacy in Preventing Hospitalizations

Eight studies[18,19,50,52,53,55,60,66] 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, 1990s, and early 2000s. The vast majority of the study populations were 65 years or older and therefore we assumed that vaccination does not reduce hospitalizations in younger adults. Calculated across the included influenza seasons, the mean efficacy of the vaccine in reducing hospitalizations for influenza and pneumonia in older adults was 26.6% (Table 1, row o).

Efficacy in Preventing Mortality

Three studies provided estimates of the effectiveness of vaccinations in preventing mortality among adults.[49,53,60] These studies were from three countries (United Kingdom,[49] Canada,[53] and the United States[60]) and among them cover all influenza seasons between 1980-1981 and 1989-1990. Two of the studies defined death as death due to any cause among individuals with influenza and pneumonia hospitalization[60] or any respiratory disease.[53] These definitions were consistent with the definition of death for mortality burden of influenza from Section D, influenza-associated mortality for all underlying causes of death. The third study defined death as any death with influenza listed as the primary or secondary cause.[49] This definition was more narrow than the definition of death for mortality burden, but we decided to include the study because the definition agreement was acceptable, there were few studies of effectiveness against mortality and this study provided an estimate for an influenza season not covered by the previous two studies, and the estimate had limited weight in our averaged effectiveness estimate. As with our incidence estimates, we created an average estimate for each included influenza season and used the average across seasons in our calculations (36.5%, row q in Table 1). One study[60] had more influence in this estimate because it covered a larger number of influenza seasons. Across the three studies, all but one study participant was 45 years of age or older. Therefore, as with hospitalizations, we assumed that effectiveness of vaccination in prevention mortality is zero for younger adults.

D4. Effectiveness

Our estimates of effectiveness of offering the vaccine in preventing each type of outcome (rows n,p and r) is calculated as adherence multiplied by the respective efficacy estimate.

D5. Quality of Additional Life Years (QALYs) Saved, CPB, for all adults

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. Three studies provided data on days of influenza-like illness among the placebo group. In

Weingarten's study of hospital employees,[62] the placebo group experienced an average of 8 days of illness; healthy, working adults in a study by Nichol et al.[86] had an average duration of 7 days per episode of upper respiratory illness; and finally, working-age adults in another study by Nichol et al.[14] had an average of 9.4 days of influenza-like illness per case. However, quality of life is unlikely to be substantially reduced over all of these days. Therefore, we approximated the average quality of life reduction from non-hospitalized cases by using our standard quality-of-life reduction of 0.30 for acute conditions[32] and an average duration of illness of 7 days per case (rows t and v).

Multiplying these estimates as shown in the source column of Table 1 yields 15,164 QALYs saved from prevented illness (row w) during ages 18-49. QALYs saved from prevented illness during ages 50-64 was 9,261 and during ages 65+ was 10,595, for total QALYs saved from prevented illness of 35,020 over all adult years for the birth cohort.

QALYs Saved Through Prevented Hospitalizations

For hospitalizations, we assign an average duration of twice the duration of non-hospitalized cases (Table 1, row y), and we use the same quality-of-life reduction for acute conditions, resulting in a total of 1,344 QALYs saved from prevented hospitalizations over all adult years in a birth cohort of 4,000,000 (row bb).

QALYs Saved Through Prevented Mortality

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 prevented during the influenza season is unknown. For most other conditions analyzed in the Prevention Priorities study, we used 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 at highest 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 in this manner for most preventive services, the potential to overstate these gains using this method is larger for influenza because the mortality component of our CPB estimate is based on mortality from all causes that happened to be concurrent with an influenza infection. Therefore, we first calculated the average life expectancy (LE) at death using the LE from life tables[29] and the age at death for conditions with the ICD-9 codes used by Thompson et al. for "underlying respiratory and circulatory deaths."[28] We then use 75% of this estimate as our base-case estimate for life expectancy gains (18.0 years for the 50- to 64-year age-group and 6.4 years for the over-64 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 of life lost would have been if we use 100% of the LE at age of premature death. Seventy-five percent 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 (Table 1, row ee) are calculated by multiplying the years gained per mortality prevented by the estimated number of influenza-associated mortalities prevented.

Summed across all ages, 35,020 QALYs saved from prevented illness, 1,344 QALYs saved from prevented hospitalizations, and 253,923 QALYs were saved from prevented deaths. Together, these estimates provide our base-case CPB estimate of 290,287 QALYs saved by offering annual seasonal influenza vaccine to a birth cohort of 4 million individuals starting at age 18 (row ff).

D6. Sensitivity Analysis for CPB

In single-variable sensitivity analysis, CPB for ages 18 and older is most sensitive to the variables related to the calculation of years of life saved: mortality rates, vaccine efficacy in preventing mortality, and average life-expectancy gained per death prevented. CPB is also somewhat sensitive to adherence. Multivariate analysis with three variables shows that combining mortality, vaccine effectiveness mortality and the average life expectancy at death provide the largest range, from a low of 132,126 QALYs to a high CPB of 713,903 QALYs.

E. Cost-Effectiveness (CE) Estimate

Our approach to estimating the cost-effectiveness of influenza vaccination for adults is methodologically comparable to the CE estimates of other services evaluated in this study. 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 because the CE estimate is built on the data points presented in Table 1. Some of the entries in the data source column in Table 2 refer to rows of Table 1.

For our CE estimate, we used Molinari et al.'s[99] study of influenza burden and cost as the source for influenza treatment cost variables. We incorporated that study's age-group-specific influenza costs (inflation adjusted to year 2012 dollars). Other cost studies were reviewed and used where appropriate as described below.

A complete birth cohort approach requires year-by-year modeling and discounting of future benefits to present value at the first year the preventive service is offered to the birth cohort (in this report, age 18). We discounted the future years of life saved from a death prevented, QALYs saved from cases prevented, costs of influenza treatment, and vaccination costs to their present value in the first year the service was offered, age 18. All discounting was at 3%.

E1. Cost-Savings from Vaccinations

Health care cost savings from seasonal influenza vaccination result from prevented cases that would have been treated in the hospital or outpatient setting. Because we did not model hospitalization for ages 18-49, health care savings for that age group result from prevented cases that would have been treated as outpatient. We used per-case cost estimates for treating influenza in the outpatient setting from Molinari et al.,[99] after inflation adjustment (Table 2, row gg). We used an average of Molinari et al.'s age- and risk group-specific outpatient costs, weighted by their estimate of outpatient cases by group. We applied these estimates to an annualized estimate of our incidence rate from our CPB calculations. We used results from four studies for our estimate that 30% of cases receive outpatient care.[4,14,85,100] Three of the estimates were for populations aged 18-64 and one was for ages 20-49. Although the studies had limitations for our purposes (they included subjects older than age 50[4,14,100] and two were from Canada and reported outpatient use for a vaccinated population only[85,100]) they offered the best guidance for our estimate. Our estimate of 30% is similar to the 36% estimate of outpatient care of Molinari et al.'s modeled 18- to 49-year-old population. To maintain consistency across preventive services analyzed in this project, we did not incorporate the indirect costs of influenza cases used by Molinari et al.

Using these assumptions, we estimate $307.5 million savings from prevented outpatient treatment due to seasonal influenza vaccination during ages 18-49. An additional $406.3 million and $485 million would be saved during ages 50-64 and 65+, respectively, for a total of $1.2 billion in savings during all adult years combined (Table 2, row jj). Discounted at 3% to age 18, the total outpatient care savings would be $421.8 million (row kk). Prevented hospitalizations would save another $697.2 million (discounted) for the 18+ age group (row nn), resulting in total discounted health care savings of $1.12 billion (row pp).

E2. Vaccination Costs

We use an average of estimates of private sector and Medicare payments for all patients. This average provides a proxy for real resource use, and is used across other preventive services in the priorities ranking. Therefore, for influenza vaccinations we use an average of the private and Medicare estimates for all ages rather than applying different estimates for ages 18-64 and ages 65 and older as might be done if our goal was to create estimates from the budgetary perspective of different payers. Private sector costs used in the average were estimated as the average of CDC private sector cost per dose of 10-dose vials, plus 75% of the median charge for vaccine administration CPT4 code 90741.[101] Limited data indicate that the market share for FluMist in the age 18- to 49-year-old age group is small enough that when combined with lower vaccine administration costs for nasal administration (CPT4 code 90743), FluMist has little impact on the average cost of influenza vaccine. Therefore we used the same cost for ages 18-49 as for ages 50 and older. Our Medicare average is derived from Medicare-allowed payments for trivalent vaccine in 2012 and vaccine administration. Our Medicare estimate does not include high-dose quadrivalent flu vaccine. ACIP does not recommend one vaccine over another for those ages 65+ (except where intranasal live vaccine is contra-indicated) and ACIP notes

that evidence on the incremental effectiveness of high-dose vaccine is limited. One study found greater protection against clinically confirmed influenza.[102] In our estimate of cost effectiveness, neither vaccination costs nor vaccine effectiveness was increased to reflect the portion of 65 and older adults who elect high-dose vaccine.

To improve consistency across the preventive services included in our study, we use a standard method of valuing time for patients to travel to the clinic and receive the service. We assume that it takes 2 hours for an office visit, but that only half of this time is attributable to the vaccination itself, because some patients receive one or more other services at the same time. We use average hourly earnings plus benefits in 2005[103] to estimate the value of patient time and inflation-adjusted that amount to 2012 dollars. The resulting estimate of the value of patient time is $31.00 in 2012 dollars per person vaccinated (row rr). This estimate is close to that used by Bridges et al.[4] ($14.70 in 1999 dollars) and within the range used by Meltzer et al. ($8 to $39 in 1995 dollars).[104]

Using these assumptions, we estimate that lifetime vaccination costs during ages 18-49 would be $5.02 billion (Table 2, row ss). Vaccination costs during ages 50-64 and ages 65+ would be $3.1 billion and $3.7 billion, respectively, for a total of $11.9 billion over the adult years of a birth cohort. After discounting at 3% to present value at age 18, lifetime vaccination costs over all ages totaled $5.02 billion (row tt).

E3. CE Calculation

The net cost of vaccination was $4.8 billion in 2012 dollars during ages 18-49, $2.1 billion during ages 50-64, and $0.5 billion during ages 65+.(Table 2, row uu). Discounted at 3% to present value at age 18, the net cost of vaccination was $3.13 billion in 2012 dollars during ages 18-49, $0.69 billion during ages 50-64, $0.09 billion during ages 65+, and $3.90 billion over all adults years in a birth cohort of 4,000,000 (row vv).

Our base-case CE of offering annual seasonal influenza vaccine to a birth cohort of 4 million individuals starting at age 18 is $69,554 per QALY saved (Table 2, row aaa). Dividing discounted net costs by discounted QALYs saved yielded a CE ratio of $313,910 per QALY saved for ages 18-49, $53,021 per QALY saved for ages 50-64, and $2,579 per QALY saved for ages 65+.

E4. Sensitivity Analysis for CE

The sensitivity analysis reported by three abstracted studies[20,60,105] 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. The fourth study reported that CE ratios were most sensitive to incidence, vaccine effectiveness, and costs of vaccination for healthy adults18 to 49 years old, but vaccine effectiveness assumptions had little effect on CE ratios for high-risk adults ages 50 to 64 or older than 65.[106]

In our CE estimate, the most important variables were the value of patient time to receive the vaccine, incidence of hospitalization, the years of life gained per death prevented, and the efficacy of the vaccine in preventing hospitalizations. Secondarily, the estimates of mortality incidence, the cost of the vaccine, the costs of hospitalization, influenza incidence rate, efficacy of the vaccine in preventing mortality, and the efficacy of the vaccine in preventing influenza-like illness were 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.[32] Simultaneously changing the duration of ILI illness and hospitalization, the ILI incidence and patient time costs produces our lower bound estimate of $26,966 per QALY saved, discounted to age 18. Simultaneously changing the value of average life expectancy at death, ILI incidence and patient time costs yields an upper bound CE ratio of $175,931 per QALY saved.

F. Limitations

Our models provided transparent estimates of the benefits and CE of offering influenza vaccine to a birth cohort of 4 million individuals starting at age 18. 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, hospitalization incidence, and years of life gained per death prevented. These data points were either not directly observed or were observed in populations that may not be generalizable to the target population across the United States.

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, comparisons of those who did and did not receive the vaccine may cause the estimates of effectiveness against hospitalizations and death to be overstated.[107-109] Results of recent studies support the argument that using diagnosis codes as covariates in observational studies does not sufficiently adjust for selection bias.[66,110] The potential impact of this bias was reduced by limiting hospitalizations to those for influenza and pneumonia and limiting deaths to those associated with influenza. In addition, we selected studies with consistent definitions of death for our estimates of the mortality burden from influenza and vaccine effectiveness against death. We did not include any studies that defined the outcome as death from any cause for our estimate of vaccine effectiveness against death. This limited but did not eliminate the potential for the estimated health impact and cost savings to be overstated.

Our estimate excluded adverse events from the influenza vaccine. Three randomized controlled trials have found no differences in systematic reactions (e.g., fever, fatigue, headaches) between vaccination and placebo groups, but they found statistically significant differences in mild localized reactions (e.g., soreness at injection site, swelling, itching).[111-113] Severe arm soreness occurred in about 2% of vaccinated individuals.[112] One or more other localized reactions occurred in about 20% of vaccinated individuals.[112] Few individuals reported reductions in quality of life after vaccination,[111,112] and there was no difference in this measure between cases and controls.[112] 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).[112] Given these data, it was reasonable to expect that localized reactions had a minor impact on quality of life when compared with 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 fewer 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-age adults, vaccinated study participants who had influenza-like illness averaged 1.3 days shorter duration of illness than unvaccinated participants.[14] There were no data on the relative severity of this marginal 1.3 days in unvaccinated participants or 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, about 16,000 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 7% (from 268,202 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[20-22,53] 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.

Finally, the 2015 updates did not include a new extensive literature review, so more recent evidence, such as evidence of vaccination effects during recent influenza seasons or any impact on vaccine administration costs from walk-in vaccination clinics in retail pharmacies was not included in this study.

Table 1. Calculation of Clinically Preventable Burden of the Influenza Vaccine Being Offered to a Birth Cohort of 4 Million Starting at Age 18.

Row label	Variable	Ages 18-49	Ages 50-64	Ages 65+	All adults (Ages 18+)	Data Source	Range for Sensitivity Analysis
	Person-years in target population						
a	Number of person-years in a birth cohort of 4 million	124,582,454	54,070,466	64,536,436		[29]	
	Influenza-like illness						
b	Annual incidence of influenza-like illness in unvaccinated individuals	0.149	0.149	0.149		[4,8-17,71]	0.05 to 0.25
c	Influenza cases in unvaccinated individuals	18,562,786	8,056,499	9,615,929	36,235,214	= a×b	
	Influenza-related hospitalizations						
d	Annual hospitalization rate for pneumonia or influenza in unvaccinated individuals	N/A	0.0010	0.0072		[4,18,19,27]	0 to 0.0002 0 to 0.002 .005 to .011
e	Number of hospitalizations for pneumonia or influenza in unvaccinated individuals	N/A	54,070	461,436	515,506	= a×d	
	Influenza mortality						
f	Annual influenza-associated mortality rate per 100,000	N/A	12.5	132.5		[28]	0 to 1.5 7.5 to 20.3 98.3 to 162.1
g	Total unadjusted influenza-associated related deaths	N/A	6,759	85,511		=(a×f) /100,000	
h	Vaccination rate in 1990s	N/A	34.2%	57.4%		[33,35,36]	+/- 25%
i	Efficacy of influenza vaccine in preventing influenza-related mortality	N/A	36.5%	36.5%		[49,53,60]	30%-50%
j	Predicted annual influenza mortality rate per 100,000 in the absence of vaccinations	N/A	14.3	167.5		= f / (1 – h×i)	
k	Predicted influenza-related mortalities in the birth cohort	N/A	7,721	108,116	115,837	= a×j / 100,000	
	Vaccine effectiveness						
l	Adherence with vaccine	60.0%	85.0%	85.0%		[43,47]	50% to 70% 75% to 95% 75% to 95%
m	Efficacy of influenza vaccine in preventing influenza-like illness	23.6%	26.6%	26.6%		[4,8-17,71]	10% to 30%
n	Effectiveness of offering vaccine in preventing influenza-like illness	14.2%	20.1%	20.1%		= l×m	

Row label	Variable	Ages 18-49	Ages 50-64	Ages 65+	All adults (Ages 18+)	Data Source	Range for Sensitivity Analysis
o	Efficacy of influenza vaccine in preventing hospitalizations for influenza and pneumonia	N/A	26.6%	26.6%		[18,19,50,52,53,55,60,66]	20% to 45%
p	Effectiveness of offering vaccine in preventing hospitalizations for influenza and pneumonia	N/A	22.6%	22.6%		= l×o	
q	Efficacy of vaccine in preventing influenza-related mortality	N/A	36.5%	36.5%		= e	
r	Effectiveness of offering vaccine in preventing mortality	N/A	31.0%	31.0%		= l×q	
	QALYs saved through prevented influenza-like Illness						
s	Predicted non-hospitalized cases prevented	2,628,490	1,605,287	1,836,391	6,070,169	= c×n	
t	Duration of illness in years (= 1 week)	0.0192	0.0192	0.0192		[32]	0.5 to 2 weeks
u	Year-equivalents of illness prevented by reduced non-hospitalized cases	50,548	30,871	35,315		= s×t	
v	Quality-of-life reduction per year (QALY weight)	0.30	0.30	0.30		[32]	0.20 to 0.40
w	QALYs saved due to reduced non-hospitalized cases	15,164	9,261	10,595	35,020	= u×v	
	QALYs saved through prevented hospitalizations						
x	Predicted hospitalizations for pneumonia or influenza prevented	N/A	12,219	104,273	116,491	= e×p	
y	Duration of illness in years (= 2 weeks)	N/A	0.0385	0.0385		See text	1 to 3 weeks
z	Year-equivalents of illness prevented by reduced hospitalized cases	N/A	470	4,010		= x×y	
aa	Quality of life reduction per year (QALY weight)	N/A	0.30	0.30		[32]	0.20 to 0.40
bb	QALYs saved due to reduced hospitalized cases	N/A	141	1,203	1,344	= z×aa	
	QALYs saved through prevented mortality						
cc	Predicted mortalities prevented	N/A	2,392	3,497	35,889	= k×r	
dd	Average life expectancy at death	N/A	18.0	6.3		see text	12.0 to 24.0 4.2 to 8.5
ee	Years of life saved	N/A	44,039	209,884	253,923	= cc×dd	
ff	**Total QALYs saved (CPB)**	15,164	53,442	221,681	**290,287**	=w+bb+ee	

Table 2. Calculation of Cost Effectiveness of the Influenza Vaccine Being Offered to a Birth Cohort of 4 million Starting at Age 18

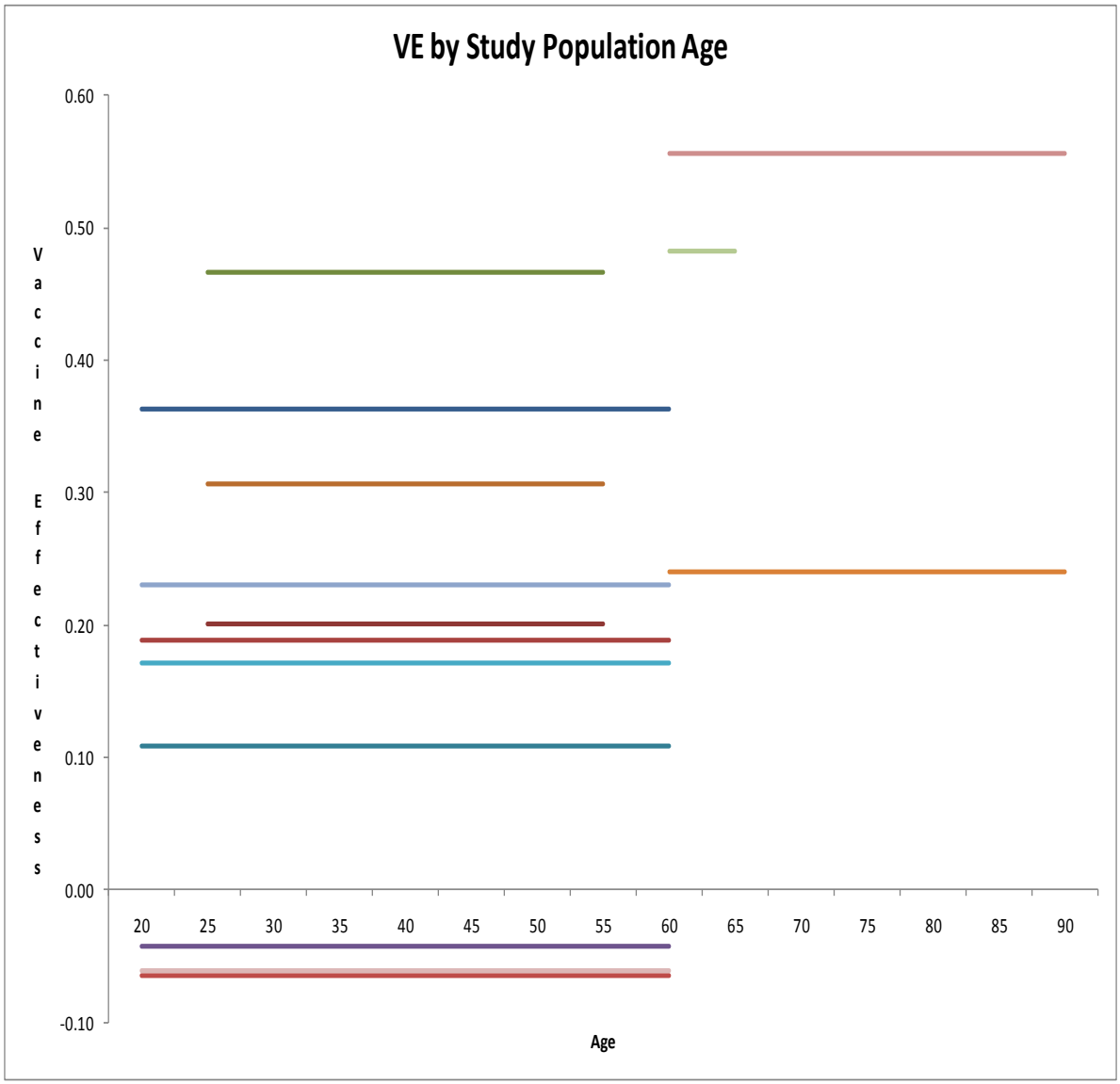
		Ages 18-49	Ages 50-64	Ages 65+	Ages 18+	Data Source	Range for Sensitivity Analysis
	Health care costs savings						
gg	Cost per outpatient treated case	$390	$559	$559		[99]	+/- 25%
hh	Percent of cases receiving outpatient care	30%	45%	45%		[4,14,85,100]	15% to 45% 25% to 55% 25% to 55%
ii	Number outpatient treated cases	5,568,836	3,625,425	4,327,168	13,521,428	= c×hh	
jj	Outpatient care case savings	$307,533,383	$406,392,999	$485,055,113	$1,198,981,494	= gg×ii×n	
kk	Discounted outpatient care cost savings	$202,494,438	$129,882,636	$89,379,888	$421,756,991		
ll	Cost per hospitalized case	N/A	$47,911	$26,549		[99]	+/- 25%
mm	Total hospitalization case savings	N/A	$585,409,637	$2,768,364,007	$3,353,773,644	= x×ll	
nn	Discounted hospitalization case savings	N/A	$187,096,146	$510,119,488	$697,215,634		
oo	Total health care cost savings	$307,533,383	$991,802,636	$3,253,419,120	$4,552,755,138	= jj+mm	
pp	Total discounted health care cost savings	$202,494,438	$316,978,811	$599,499,376	$1,118,972,625	= kk+nn	
	Vaccination costs						
qq	Per vaccination healthcare costs	$36.80	$36.80	$36.80		[114-116]	+/- 25%
rr	Per vaccination patient time and travel costs	$31.00	$31.00	$31.00		[103]	$13.00 to $43.33
ss	Lifetime vaccination costs	$5,067,777,525	$3,115,935,394	$3,719,061,099	$11,902,772,018	= a×l×(qq+rr)	
tt	Discounted lifetime vaccination costs	$3,336,862,988	$995,848,832	$685,302,055	$5,018,013,875		
	Cost effectiveness						
uu	Net costs	$4,760,244,142	$2,124,132,759	$465,641,979	$7,350,018,880	= ss-oo	
vv	Discounted Net costs	$3,134,368,550	$678,870,021	$85,802,679	$3,899,041,250	= tt-pp	
ww	Discounted QALYs saved from prevented non-hospitalized cases of influenza-like illness	9,985	2,960	1,952	14,897		
xx	Discounted QALYs saved from prevented hospitalizations	N/A	45	222	267		
yy	Discounted life-years saved from prevented deaths	N/A	9,799	31,095	40,894		
zz	Total discounted QALYs saved	9,985	12,804	33,269	56,058	= ww+xx+yy	
aaa	**Cost effectiveness**	313,910	53,021	2,579	69,554	= yy/zz	

Table 3. Sources and Estimates Used for the Influenza-like Illness Estimates ages 50+

Source	Influenza season	Incidence of influenza-associated		Vaccine effectiveness to prevent Influenza-associated			Outcome or population or vaccine
		Influenza-like Illness	Hospitalization	Mortality	Influenza-like Illness	Hospitalization	
Ahmed, 1995[49]	1989-90			0.410			
Ahmed, 1997[50]	1989-90					0.630	
Allsup, 2004[8]	1999-00	0.011			0.200		GP diagnosed
	1999-00	0.089			0.480		Self-diagnosed
Barker, 1980[52]	1968-69					0.077	
	1972-73					0.739	
Beran, 2009	2005-06	0.056			-0.060		
Bridges, 2000[4]	1997-98	0.238			-0.100		ILI
	1997-98	0.419			-0.030		URI
	1998-99	0.215			0.330		ILI
	1998-99	0.262			0.130		URI
Davis, 2001[19]	1994-97		0.008			0.000	
Edwards, 1994[10]	1987-88	0.246			0.038		inactivated
	1987-88				0.180		cold adapted
	1988-89	0.213			0.222		inactivated
	1988-89				0.150		cold adapted
	1989-90	0.144			-0.055		inactivated
	1989-90				-0.030		cold adapted
Fedson, 1993[53]	1982-83			0.650		0.320	
	1985-86			0.540		0.380	
Foster, 1992[55]	1989-90					0.330	
Govaert, 1994[11]	1991-92	0.034			0.470		Family physician
	1991-92	0.098			0.310		Sentinal stations
	1991-92	0.142			0.170		ICHPPC-2-defined

Source	Influenza season	Incidence of influenza-associated		Vaccine effectiveness to prevent Influenza-associated			Outcome or population or vaccine
		Influenza-like Illness	Hospitalization	Mortality	Influenza-like Illness	Hospitalization	
Jackson, 2006[66]	1995-02 excl 1999, 2000					0.000	
Kawai, 2003[12]	2001-02	0.018			0.680		Ages 18-65
	2001-02	0.007			0.190		Ages 65+
Keitel, 1997[13]	1983-84	0.050			0.000		
	1984-85	0.033			0.060		
	1985-86	0.091			0.200		
	1986-87	0.065			0.470		
	1987-88	0.097			0.310		
Mullooly, 1994[60]	1980-81 through 1988-89			0.330		0.300	High-risk
	1980-81 through 1988-89					0.400	Non–high-risk
Nichol, 1999[14]	1997-1998	0.168			0.100		Febrile illness
	1997-1998	0.137			0.180		Severe febrile illness
	1997-1998	0.121			0.230		Febrile URT illness
Nichol, 2007[18]	1990-91 through 1999-00		0.0070			0.270	
Nichol, 2008[15]	2002-06	0.255			0.300		
Praditsuwan, 2005[16]	1998-99	0.109			0.560		
Waldman, 1969	1967-68	0.278			0.060		A2/Hong Kong injection
	1967-68				0.310		bivalent injection
	1967-68				0.310		A2/Hong Kong aerosol
	1967-68				0.240		bivalent aerosol

Figure 1. Vaccine Effectiveness by Study Population



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