REVIEW ARTICLE

Drugs 2012; 72 (1): 35-48
0012-6667/12/0001-0035/$55.55/0

Seasonal Influenza Vaccination of Healthy Working-Age Adults

A Review of Economic Evaluations

Justin Gatwood,[1] *Martin I. Meltzer,*[2] *Mark Messonnier,*[2] *Ismael R. Ortega-Sanchez,*[2] *Rajesh Balkrishnan*[1] and *Lisa A. Prosser*[3]

1 University of Michigan College of Pharmacy, Ann Arbor, MI, USA
2 Centers for Disease Control and Prevention, Atlanta, GA, USA
3 University of Michigan Medical School, Ann Arbor, MI, USA

Contents

Abstract

The recent impact of influenza on the working-age population of the US has led to changes in the recommendations for vaccination against seasonal influenza; however, the implications of vaccinating such a population have been debated. A review of cost-effectiveness analyses of vaccinating the working-age population of the US against seasonal influenza was conducted using articles published between January 1990 and January 2010. Studies considered for

inclusion were identified using MEDLINE, EMBASE and Econlit. Reviewers worked in pairs, and each team member independently extracted relevant data using a standard abstraction form. The source and appropriateness of parameters (epidemiological data, probabilities and costs), the designs employed and the sufficiency of sensitivity analysis were considered during review. Key inputs extracted from the selected studies included influenza or influenza-like illness attack rates, outpatient visits averted, total vaccination days and lost workdays.

Seven studies were identified as appropriate for this review. All studies were conducted in the US and from the societal perspective; three were randomized controlled trials and the remaining four were economic simulation models comparing vaccination and influenza antiviral drugs or no intervention; analyses focused on healthy working-age adults aged 18–49 years. Results ranged from net savings of $US68.96 to net costs of $US85.92 per person vaccinated (four studies) and net costs of $US104–1005 per episode of influenza averted (one study). Only two studies reported cost-effectiveness ratios; these ranged from $US26 565 to $US50 512 per quality-adjusted life-year gained. Nearly all of the studies conducted sensitivity analysis; results were most sensitive to variation in wage rates, levels of worker productivity, the costs and effectiveness of vaccination, and the rate of influenza illness. Review of the included studies suggests that seasonal influenza vaccination of healthy, working-age adults is generally not cost saving, requiring an investment to generate health benefits. The decision to vaccinate such a group will depend upon the societal and payer valuation of those benefits.

1. Background

In February 2010, the Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) voted on a new recommendation for vaccination against seasonal influenza that now recommends routine annual influenza vaccination for all individuals aged ≥6 months.[1] Prior to this meeting, the ACIP focused the annual recommendation on higher-risk populations of the US: children aged 6 months to 19 years, adults aged ≥50 years, pregnant women, those with immunosuppression or certain chronic conditions, and those in close contact with high-risk individuals. These recommendations covered approximately 85% of the US population.[1,2]

The costs and benefits of vaccinating working-age adults have been debated. The ACIP first recommended that a portion of this population be vaccinated against seasonal influenza in 2000 when adults aged ≥50 years were added to the annual recommendations.[3] The purpose of this study was to conduct a review of published economic analyses of vaccinating the most recently added subgroup: healthy, working-age adults aged 18–49 years in the US.

2. Methods

2.1 Search Strategy

Studies considered for inclusion in this review were identified using MEDLINE, EMBASE and Econlit databases. We used the search terms 'influenza', 'vaccination', 'seasonal', 'cost-benefit' and 'cost-effectiveness' to identify studies published between January 1990 and January 2010. Furthermore, to be included, papers had to have been published in a peer-reviewed journal and focus on a population that included healthy adults aged 18–49 years, and be set in the US.

2.2 Data Extraction

We initially identified 13 published papers that met our criteria. A group review of the 13 studies determined that six studies focused primarily on

costs and did not include an evaluation of health benefits from vaccination. They were removed from the pool of included papers. Data were then extracted from the seven remaining articles using a standard abstraction form. The abstraction form was developed by considering parameters included in previous CDC reviews, the Drummond et al.[4] checklist categories and review group consensus. Each paper was abstracted independently by two reviewers. When data abstracted from different reviewers did not agree, consensus was reached by discussion. The following categories were used for extraction: author, publication, year, country, study type, perspectives employed, model elements, comparison method, main epidemiological and clinical data, main disease and vaccine cost data sources, quality-of-life adjustment, vaccine, adverse events, sensitivity analyses, main outcomes reported, policy implications, and strengths and limitations (table I). Following agreement, the selected studies were compiled into a final spreadsheet to be used for comparison in this study and all economic values were adjusted to $US, year 2010 values, for this review using the Consumer Price Index (CPI).[5] Although the mix of direct and indirect costs complicates the selection of an inflation adjustment approach, we believe the CPI-adjusted values would be the closest to the 'real' societal costs, mainly because indirect costs, usually adjusted using the CPI, tend to be the largest component (>68%) of total influenza costs.[6]

3. Results

3.1 Study Design

3.1.1 Type of Study

Five of the included studies were cost-benefit analyses and two were cost-effectiveness analyses.

The designs used by the studies showed considerable variability. Three of the investigations were randomized, placebo-controlled trials (RPCT) involving healthy adults aged 18–64 years;[7-9] a fourth employed second-order Monte Carlo simulation to assess the mean costs and benefits of seasonal vaccination.[10] The remaining three selected studies used decision tree models[11-13] (table II).

Table I. Data extraction elements

Categories	Additional elements
Author	
Publication	
Year	
Country	
Study type	
Perspectives employed	
Model elements	Model design, targeted population, herd immunity, costing year, discount rate, time horizon
Comparison method	Strategy of intervention/provider base, comparator/baseline
Main epidemiological and clinical data	Incidence measurement, mortality/case fatality rate, hospitalization rates, outpatient/emergency room visit rates, additional illnesses rates, epidemiological data source
Main disease and vaccine cost data sources	Medical cost, indirect cost, intervention cost
Quality adjustment	Sources
Vaccine	Number of doses, efficacy
Adverse events	Probability of moderate event, cost of moderate event, probability of severe event, cost of severe event
Sensitivity analyses	Main variables in the sensitivity analysis, type of sensitivity analysis
Main outcomes reported	Effectiveness outcome reported, type of ratio or net value reported, value of ratio as reported, value of ratio converted to $US, year 2004 values, consumer price index for conversion or real exchange rate
Policy implications	Strategy enhancing vaccine access, strategy increasing vaccine demand, strategy applicability
Strengths and limitations	Suitability of study design, limitations identified, acceptability for this review, comments for rejection or acceptance

Table II. Model elements of health economic studies of influenza vaccination in healthy adults

Study (y of publication)	Model design	Targeted population	Perspectives	Time horizon	Study type	Compared alternative(s)
Bridges et al.[8] (2000)	RCT	Healthy working adults, aged 18–64 y	Societal and payer	1 y	CBA	Placebo
Lee et al.[11] (2002)	Linear cohort (probabilistic)	Healthy working adults, aged 18–50 y	Societal	Influenza season	CBA	Vaccination plus an antiviral; antiviral alone; no treatment
Nichol et al.[9] (2003)	RCT	Healthy, aged 18–64 y	Societal	Influenza season	CBA	Placebo
Nichol[10] (2001)	Monte Carlo Simulation	Healthy, aged 18–64 y	Societal	Life expectancy for indirect costs; influenza season for direct costs	CBA	No vaccination
Nichol et al.[7] (1995)	Linear population/RCT	Aged 18–64 y	Societal	1 y	CBA	Placebo
Prosser et al.[13] (2008)	Decision tree math model	18–49 y (HR); 18–49 y (healthy); 50–64 y (HR); 50–64 y (healthy); ≥65 y (all risks)	Societal	1 y, lifetime for mortality effects	CEA	No vaccination
Rothberg and Rose[12] (2005)	Markov model	Healthy working adults, aged <50 y	Societal	Influenza season	CEA	Vaccination plus an antiviral; antiviral alone; no treatment

CBA = cost-benefit analysis; **CEA** = cost-effectiveness analysis; **HR** = high risk; **RCT** = randomized controlled trial.

3.1.2 Site of Vaccination

In most of the studies, worksite was the site of vaccination. Prosser et al.[13] also considered the pharmacy and physician office settings. Similarly, Nichol[10] assumed that, in addition to worksite clinics, vaccination could also take place in health departments, drug stores and supermarkets. As a result, related costs of the approaches used by these assessments were appropriately included so that outcomes reflected the added financial burden of these procedures. Additionally, as part of a RPCT trial, Nichol et al.[9] allowed for study subjects to directly administer the live attenuated influenza vaccine (LAIV).

3.1.3 Comparator Strategies

The base-case intervention in each study was either no vaccination or vaccination with placebo. However, Lee et al.[11] and Rothberg and Rose[12] also incorporated effects of antiviral medications on economic outcomes in their studies. Lee et al.[11] compared annual vaccination with no vaccination, allowing for the use of antivirals (rimantadine, zanamivir or oseltamivir) or no treatment if clinically ill, incorporating eight treatment options into the model. Alternatively, Rothberg and Rose[12] assessed vaccination compared with no vaccination, and included the use of one of two antiviral drug strategies (amantadine or rapid testing followed by oseltamivir if required) upon symptom presentation. Prosser et al.[13] compared four strategies: no vaccination and vaccination by inactivated influenza vaccine in a physician office setting, mass vaccination setting or pharmacy. Additionally, Rothberg and Rose[12] used a Markov model to compare annual vaccination and antiviral therapy with no intervention over 10 years (table II).

3.1.4 Target Population

Target populations in the included studies ranged from 18 to 64 years, although some studies restricted the analysis to adults aged 18 to 49 or 50 years. Baseline characteristics of the patient populations involved in the Nichol et al.[7,9] RPCTs were balanced for all characteristics assessed, including gender proportions and educational levels, with a mean age of 39 years. Baseline characteristics were generally balanced in the study by Bridges et al.[8]

but, due to the population employed (full-time employees of the Ford Motor Co., Dearborn, MI, USA), their study had a higher percentage of male participants and higher income earners as well as a higher mean population age than the Nichol et al.[7,9] investigations. The remaining studies merely assessed the effect of vaccination across the entire range of ages for healthy working adults without consideration for differences in clinical outcomes that may occur due to increased age. One study (Prosser et al.[13]) stratified the analysis by age and risk status, allowing for the assessment of high-risk individuals in comparison with healthy adults in the study's cohort (table II).

3.1.5 Perspective of the Analysis

All of the selected studies provided examinations from the societal perspective. This approach allows for the inclusion of indirect costs related to the labour market, such as productivity loss and work days gained or lost as a result of the intervention. In addition to this, Bridges et al.[8] also provided analysis from the perspective of the healthcare payer. This perspective excluded illness-related costs such as co-payments, over-the-counter medications, and any valuation of lost work time (table II).

3.1.6 Clinical Outcomes

Clinically relevant outcomes of the reviewed studies included upper respiratory illness, febrile illness, influenza-like illness (ILI) and rates of laboratory-confirmed influenza. Patient-reported outcomes of ILI were used in two of the clinical trials,[8,9] while laboratory-confirmed cases supplemented this information in the third.[7] Otherwise, surveillance information and data from previous studies were used in modelling.[10-13] Only two studies gave consideration to the impact of both hospitalization and mortality on outcomes in the analysis;[10,13] a third only considered the effect of hospitalization rates[12] (table III).

3.1.7 Economic Endpoints

Economic endpoints showed considerable variation among the studies. Both Nichol et al.[7] and Bridges et al.[8] reported economic outcomes in terms of net returns per person vaccinated. In subsequent papers, Nichol and colleagues reported economic findings as net costs per person vaccinated (2001)[10] and then as break-even values for direct costs of vaccination.[9] Lee et al.[11] reported results as benefit-cost ratios based on a willingness-to-pay survey. Prosser et al.[13] presented outcomes in the form of dollars per outcome averted and included influenza episodes, hospitalizations and deaths. Rothberg and Rose[12] reported outcomes as dollars per quality-adjusted life-years (QALY) based on quality-adjusted life-days of the study population using willingness-to-pay parameters (table IV).

Taken from a societal perspective, results ranged from net savings to net costs of $US85.89 per vaccination (four studies) and from $US104 to $US1005 per episode of influenza averted (one study); cost-effectiveness ratios ranged from $US26 565 to $US50 512 per QALY gained.[7-13] Bridges et al. determined that, when assessed from the perspective of the healthcare payer, money would not have been saved by vaccinating.[8]

Results were also given for cohorts within the included studies. Stratified by age and risk status, results for healthy adults aged 18–49 years were not cost saving in any of the settings using base-case values.[13] However, Monte Carlo simulation in another model resulted in a net savings of $US18.29, with a best-case scenario of $US233 in savings by vaccinating.[10] Additionally, based on comparison with no vaccination or antiviral therapy, the combination of rimantadine and vaccination resulted in the most cost-beneficial strategy using mean willingness-to-pay values. Analysis indicated that this led to a net benefit of $US38.16.[11] Also, comparing vaccination with antiviral therapy alone in the assessment by Rothberg and Rose[12] led to an incremental cost-effectiveness ratio of $US50 512 per QALY. Table IV summarizes the economic results reported within each study.

3.2 Key Parameters and Assumptions

3.2.1 Vaccine Effectiveness

A variety of approaches was used to establish vaccine effectiveness in each of the included studies. Each of the clinical trials used their respective datasets to calculate effectiveness of either LAIV or inactivated influenza vaccination.[7-9] Values of

Table III. Epidemiological and clinical data assumptions of health economic studies of influenza vaccination in healthy adults

Study (y of publication)	Incidence measurement (%)	Mortality/CFR rates per 100 000	Hospitalization rates per 100 000	Outpatient/ER visit rates, per 100	Vaccine efficacy (%)[a]
Bridges et al.[8] (2000)	ILIs 1997–8 Unvaccinated: 24 Vaccinated: 28 1998–9 Unvaccinated: 22 Vaccinated: 14	Not included	NA	1997–8 Unvaccinated: 9 Vaccinated: 11 1998–9 Unvaccinated: 9 Vaccinated: 5	1997–8: 50 1998–9: 86
Lee et al.[11] (2002)	Unspecified: 15	NA	NA	NA	68
Nichol et al.[9] (2003)	Rate of febrile illness observed and modelled from LAIV trial	NA	NA	5	Reduction in work loss: 18 Reduction in days working at reduced effectiveness: 18 Reduction in HCP visits: 13
Nichol[10] (2001)	Clinical influenza rate: 5	1	40	45	Good match: 75 Poor match: 35 Chance of good match: 80
Nichol et al.[7] (1995)	Primary trial data (per 100 subjects) URI attack rate: 105 URI physician visits: 31 URI lost work days: 70	NA	NA	55 (placebo) 31 (vaccine)	URI: 25 URI physician visits: 44 URI lost work days: 43
Prosser et al.[13] (2008)	18–64 y Clinical influenza illness: 6.6	18–49 y: 0.22 50–64 y: 3	18–49 y: 14 50–64 y: 44	31	69
Rothberg and Rose[12] (2005)	ILI per week: 2	No deaths	Given influenza: 400	Given ILI: 40	72

a Vaccine efficacy was defined as follows: laboratory-confirmed illness;[8,10,11,12,13] reduction in febrile illness symptoms;[9] differences between vaccine and placebo groups in terms of episodes of URI, days of sick leave due to URI and visits to a physician as a result of URI.[7]

CFR = case fatality rates; **HCP** = healthcare provider; **ILI** = influenza-like illness; **LAIV** = live attenuated influenza vaccine; **NA** = not applicable; **URI** = upper respiratory illness.

vaccine effectiveness for each of the respective clinical outcomes ranged from 20% to 89%, as compared with placebo; methods of calculating vaccine effectiveness in each study led to the wide variation in results.[7-9] However, only one of the trials used laboratory-confirmed cases of influenza illness to determine vaccine effectiveness;[8] self-reported illness was used otherwise (table III).

Multiple methods of setting vaccine effectiveness were used to model the remaining studies. Values from a previously published Australian investigation were used by Nichol[10] in the 2001 cost-benefit analysis to establish a base-case vaccine effectiveness of 75% in years with a good match of strains – the likelihood of a good match was 80%.[14] Otherwise, the vaccine effectiveness was assumed to be 35% in years with a poor match of influenza strains in the vaccine. Rothberg and Rose[12] considered both these estimates and several years of CDC surveillance data regarding circulating influenza strains, and used a value of 72% effective. Prosser et al.[13] and Lee et al.[11] also considered the results from two of the clinical trials and used vaccine effectiveness estimates ranging from 68% to 75% (table III).

3.2.2 Incidence of Clinical Outcomes

There was considerable variation between studies in the likelihood of influenza illness. In the papers that used economic models, annual rates of illness ranged from 5% to 15% for clinical cases of influenza and from 6% to 10% for ILI, although most base-case values were below 10%.[10-13] In one instance, disease severity was allowed to reach 35% during sensitivity analysis;[11] however, the upper limit for most models peaked at a disease

Table IV. Outcomes of health economic studies of influenza vaccination in healthy adults

Study (y of publication)	Clinical and economic outcomes	Economic endpoint	Value of ratio as reported ($US)	Type of sensitivity analysis	Variables in the sensitivity analysis
Bridges et al.[8] (2000)	Cases prevented, outpatient visits saved, hospitalizations prevented, in-hospital deaths prevented, days of work gained	Net cost	*Societal perspective* 1997–8: 85.92 per person vaccinated 1998–9: 14.63 per person vaccinated *Healthcare perspective* 1997–8: 41.13 per person vaccinated	Univariate	Labour costs, vaccination cost (time), ILI attack rates
Lee et al.[11] (2002)	WTP for symptom relief and side effects avoided, workdays gained	Benefit-cost ratios	38.16 : 1 for vaccination and rimantadine if infected 36.34 : 1 for vaccination and no antiviral if infected	One-way; probabilistic	All variables
Nichol et al.[9] (2003)	Reduction in work days lost, work at reduced effectiveness, healthcare provider visits	Break-even values	57.67 per person vaccinated	Monte Carlo	All variables
Nichol[10] (2001)	Illness, absenteeism, work effectiveness, physician office visits, hospitalization, deaths	Net cost per person vaccinated	–18.29 per person vaccinated	Minimum/maximum; scenario	All variables
Nichol et al.[7] (1995)	Net cost	Net savings	68.96 per person vaccinated	NA	NA
Prosser et al.[13] (2008)	$ per influenza episode prevented, hospitalization prevented and death averted	ICERs	*Pharmacy setting* CS–104 per episode averted CS–50 820 per hospitalization averted CS–4 966 500 per death averted *Mass vaccination setting* CS–243 per episode averted CS–115 500 per hospitalization averted CS–11 319 000 per death averted *Physician office setting* 474–1005 per episode averted 66 990–473 550 per hospitalization averted 924 000–45 738 000 per death averted	One-way; probabilistic	All variables
Rothberg and Rose[12] (2005)	Costs, illness days, hospitalizations, lost workdays, physician office visits	$ per QALY	50 512 per QALY gained	One-way and multi-way; probabilistic	Only select variables described

CS = cost saving; **ICERs** = incremental cost-effectiveness ratios; **NA** = not applicable; **QALY** = quality-adjusted life-year; **WTP** = willingness to pay.

prevalence of 15%. Epidemiological information used by the authors of the included studies was obtained through literature reviews, including clinical trials reviewed herein, or from surveillance reports (table V).

Additionally, several studies also included rates of hospitalization due to influenza illness, and base-case values for this parameter differed substantially across studies. Prosser et al.[13] assumed hospitalization rates of 14–218.3 per 100 000 in healthy adults aged 18–49 years. Nichol[10] reported a rate of 40 per 100 000 while Rothberg and Rose[12] used a baseline probability of 400 per 100 000. Although two of the clinical trials were not powered to analyse differences in hospitalization rates, Bridges et al.[8] did report this as a clinical outcome; only two hospitalizations were reported during the 2 years of the trial (table III).

3.2.3 Costs

All analyses were conducted using the societal perspective; therefore, both direct and indirect costs were considered in each. Costs in each study were adjusted according to a recent CPI. Only Nichol[10] explicitly mentioned discounting values; however, the use of discounted values was not necessary in other trials, as the value of lost future income was not applicable to the time horizon of those studies.

Costs of Vaccination

Total vaccine administration costs ranged from $US6.13 to $US34.55;[7-13] variations were mainly dependent on the assumed site of vaccination and the source of cost data. The lowest value given for the cost of vaccination was provided by Nichol et al.,[9] but their calculation lacked inclusion of direct costs of administering the vaccine, claiming that the costs of LAIV were unknown at the time. In the other included studies, both surveys or interviews and established clinical trial data were used to construct the costs of administering the vaccines; however, it should be noted that two of the included studies (Nichol et al.,[9] Nichol[10]) relied on the estimate

Table V. Health economic and epidemiological data sources

Study (y of publication)	Medical cost	Indirect cost	Intervention cost	Epidemiological data
Bridges et al.[8] (2000)	Survey; MEDSTAT	US Bureau of Labor Statistics	Secondary literature	Serological; patient report
Lee et al.[11] (2002)	Secondary literature	US Bureau of Labor Statistics	Secondary literature	Secondary literature
Nichol et al.[9] (2003)	HCA Physician Fee and Coding Guide (1997); NAMCS (1994, 1995); Red Book	US Bureau of Labor Statistics; secondary literature	LAIV trial	Observed and modelled from LAIV trial; NHAMCS; NAMCS
Nichol[10] (2001)	Secondary literature (MEDSTAT, HCUP, NAMCS)	US Census Bureau	American Lung Association, Minnesota, USA	Secondary literature; CDC
Nichol et al.[7] (1995)	1994 AMA Socioeconomic Monitoring System Core Survey; 1992 National Ambulatory Care Survey; 1993 Physician Payment Review Commission Multipayer Database; survey for OTC costs	Participant report, US Labor average wage and benefit	Survey	Primary data
Prosser et al.[13] (2008)	Insurance database (MEDSTAT)	Secondary literature	Primary telephone interviews	Secondary literature; expert panel
Rothberg and Rose[12] (2005)	Secondary literature	US Bureau of Labor Statistics	Secondary literature	Secondary literature

AMA = American Medical Association; **CDC** = Centers for Disease Control and Prevention; **HCA** = Healthcare Consultants of America; **HCUP** = healthcare cost and utilization project; **LAIV** = live attenuated influenza vaccine; **NAMCS** = national ambulatory medical care survey; **OTC** = over the counter.

Table VI. Costs of health economic studies of influenza vaccination in healthy adults ($US, year 2010 values)

Study (y of publication)	Disease costs			Intervention costs			Costing year
	Outpatient visit	Hospitalization	Indirect	Vaccination	Moderate adverse event (rate per 1000)	Severe adverse event (rate per 1 000 000)	
Bridges et al.[8] (2000)	139.08	10 206	307.98 per day 38.50 per visit	32.36	NA	NA	1999
Lee et al.[11] (2002)	33.26	NA	490.19 per event	23.77	NA	NA	2001
Nichol et al.[9] (2003)	163.36	NA	160.68 per day	6.13 (indirect only)	2.79 (provider visits: 5; workdays lost: 10)	NA	1998
Nichol[10] (2001)	136.58	7591	321.36 per event	22.35	2.83 (provider visits: 5; workdays lost: 10)	GBS: 148 192 (1)	1998
Nichol et al.[7] (1995)	102.32	NA	137.48 per day	27.09	377.29 (medical care: 10; workdays lost: 20)	NA	1994
Prosser et al.[13] (2008)	150.15	22 921	Uncomplicated illness per episode: 82.00 Medically attended per episode: 224.69 Hospitalization per episode: 1141.51	Pharmacy: 17.56 Mass vaccination: 23.69 Traditional setting: 34.55	Systemic reaction: 150 (11)	GBS: ≥72 653 [39.68 days lost (1)] Anaphylaxis: ≥499 [2.09 days lost (1)]	2004
Rothberg and Rose[12] (2005)	Office: 56.67 ED: 197.12	4513	414.32 per event 959.48 per hospitalization	12.16	NA	GBS: 153 676 (1)	2001

ED = emergency department; **GBS** = Guillain-Barre syndrome; **NA** = not applicable.

given by Nichol et al.[7] in their 1995 clinical trial. When the indirect costs of patient time were included in the calculation of total vaccine administration costs, secondary sources from the literature were generally used as well as US labour rates, participant reporting and census data. Such indirect costs of vaccination ranged from $US1.43 to $US19.26 (table VI).[7-13]

The cost of Guillian Barre syndrome (GBS), a rare side effect associated with vaccination, was only mentioned by three of the studies, in which the cost of treating this condition ranged from $US72 653 to $US153 676 based on inflation-adjusted dollars and, according to Prosser et al.,[13] resulted in the loss of 39.68 days of productivity.[10,12] Anaphylaxis was also mentioned as a severe adverse event by Prosser et al.,[13] and the costs associated with this condition were estimated to be $US499 plus 2.09 days of lost productivity. Less severe vaccine-related adverse events were reported in some of the studies, values of which ranged from $US2.79 to $US377.29.[7,9,10,13] The rate of productivity loss related to such adverse events was estimated to be between 10 and 20 days per 1000 people.[7,9,10,13]

Costs of Illness

Medical costs included those associated with treating influenza or ILI. Related medical costs included physician visits, over-the-counter medication, prescription drugs, diagnostic tests and hospitalizations. Across all included studies, the cost of outpatient visits ranged from $US33.26 to $US163.36;[7-13] the cost of an emergency department visit was mentioned by one study (Rothberg and Rose[12]) and estimated to be $US197.12. When detailed, the cost of hospitalization to treat influenza ranged from $US4513 to $US26 890, although the majority of studies reported values below $US10 200.[8,10,12,13]

All of the studies included the economic impact of influenza vaccination on workdays, either by examining reduced lost time, hours gained or work loss avoided. The calculation of these indirect costs mirrored the methods previously described and were reported on a per day, episode or event basis (table VI). One study also included the values of reduced work effectiveness for ill

employees who do not stay home due to illness. That study used an average reduction of 50% in work effectiveness.[9,15] Additionally, two studies (Nichol,[10] Prosser et al.[13]) reported future lost earnings due to the rare event of influenza-related death in this population, and estimates were $US1 021 657 and $US1 587 103, respectively.

3.2.4 Sensitivity Analyses

All but one of the included studies (Nichol[7]) performed sensitivity analysis on the main parameters. Half of the studies that varied parameters used either multiway, probabilistic or univariate approaches, and combinations of these were also used in some instances. For cases where all study parameters were not varied, variables in the sensitivity analysis included labour cost, cost of vaccination, ILI attack rates, productivity levels, probability and costs of a physician visit, lost work time and work effectiveness. Probabilistic analyses generally used triangular distributions for parameter variation. Most studies that used some form of probabilistic analyses presented results with accompanying 95% confidence intervals.

Outcomes were responsive to variation in the wage rates of those vaccinated, the rate of illness, workdays lost due to illness, the level of worker productivity, and the cost of vaccination as well as its effectiveness. Only one study (Lee et al.[11]) reported that the model was not sensitive to changes in most variables over the ranges assessed. Of the variables shown to impact outcomes, changes in parameter values for the rate of illness, applied wage rate and the number of workdays lost had the greatest impact on results.

Results of the sensitivity analyses indicated that seasonal influenza vaccination for healthy adults aged 18–49 years could be cost saving in certain circumstances. For instance, in one study, when the probability of illness (i.e. influenza attack rate) exceeded 6.3% in a given year then the benefits of vaccinating exceeded the costs when compared with a strategy of no vaccination.[11] Similarly, Rothberg and Rose[12] determined that vaccination was cost saving in years when the annual infection rate exceeded 8%. Estimates have suggested that the influenza attack rate in working-age adults can range from 2.6% to 15.5%,[6] but rates are generally less than 10%.[8] Higher rates of illness also led to cost savings in a mass vaccination clinic according to Prosser et al.,[13] although improving the effectiveness of the vaccine to 90% failed to be cost saving for healthy adults aged 18–49 years regardless of the setting. Monte Carlo simulation in one study (Nichol et al.[9]) determined that vaccination could be cost saving 95% of the time when the mean costs of vaccination and administration were $US34.81 or less; another found that vaccination was similarly cost saving across the entire range of the probability distribution used to establish net costs.[10] Additionally, varying hourly wage rates proved to result in the widest range of mean break-even values (i.e. when vaccination costs just equalled value of benefits), from a low of $US34.12 to a high of $US89.71.[9]

4. Discussion

4.1 Overall Results

Results from this review indicate that vaccinating the healthy, working-age population of the US is generally not cost saving. More favourable economic results were reported for higher illness rates, lower costs of vaccination and higher wage rates. Several studies demonstrated that providing vaccination in lower-cost settings, such as worksite vaccination, could result in more favourable economic results. Direct savings per patient were realized in two trials; however, one of these trials failed to include values for both severe adverse events and hospitalizations since none were reported in the clinical trial.[7] The omission of hospitalization and severe adverse event costs also contributed to favourable cost-benefit ratios and break-even points in two separate studies,[10,11] the first modelling an entire influenza season and the second utilizing primary data. Generally, net societal costs or relatively high cost-effectiveness ratios per QALY were found when vaccinating healthy working-age adults, although the wide range of parameters used may lead to differences in results.

4.2 Parameter Estimates

The importance of proper parameter estimation and selection has been cited in other critical reviews and is equally applicable to the studies reviewed herein.[16] Of seven included studies, four definitions of influenza-related outcomes were used in six studies (ILI, clinical influenza, upper respiratory illness and febrile illness) and, in one study, the definition was left unspecified. Caution should be exercised in the use of ILI and other unspecific rates of influenza infection as a measurement of disease incidence; surveillance estimates from clinical illness rates may instead provide a more accurate measurement of the burden of disease. Additionally, the use of ILI as a health outcome requires the use of a lower rate of vaccine effectiveness in parameter estimates.[10] Rates of influenza illness varied widely across studies and led to a wide variation in economic outcomes; higher rates of illness were associated with more favourable economic outcomes. Defining an exact attack rate of influenza in this population is a key issue for such economic analyses since, as was observed in the included studies, these rates may significantly impact on the resulting cost-benefit ratios. Other studies have also reported a range of values for attack rates in this population due to the annual variation that exists.[6] Interpretation of results based on a single parameter estimate must be taken with caution; consideration of results following sensitivity analysis of attack rates may provide a better interpretation due to the difficulty by which even an average attack rate may be determined. Moreover, the variation in rates of outpatient visits attributable to influenza, included in most studies, was notable. Considering the related cost of these visits, such a discrepancy may have led to biased results in some instances. Similarly, the high cost of hospitalization due to influenza may also skew results. The values assumed by Prosser et al.[13] were especially high, despite being derived from the same database used by other investigations; however, these especially high costs are the result of detailing hospitalization charges specifically to the treatment of influenza/pneumonia cases.

Another key issue for readers of influenza vaccination economic analyses to consider is whether or not the estimates of vaccine effectiveness have been matched correctly to clinical outcomes.[10] For example, a study that uses ILI as the endpoint will have a lower vaccine effectiveness than a study that is modelling influenza-specific illnesses. It should also be noted that the models employed by the included studies only accounted for outcomes that were the direct impact of vaccination in immunized individuals; none of the studies examined the potential health benefits in the form of herd immunity. The potential impact that influenza vaccination of other groups, such as children, may have on working-age members should be considered by future investigations, results of which may indicate the effects of changing vaccination policies targeted at particular groups of the US population.

Clinical outcomes other than uncomplicated influenza illness, such as hospitalization, adverse events and deaths (including their respective cost estimates), were absent from at least four studies. While rates of influenza-related hospitalizations and deaths remain comparatively low in the working-age population, these outcomes, in addition to vaccine-related adverse events, are sources of lost productivity for this cohort and could be important in determining prospective cost effectiveness or cost savings from seasonal influenza vaccination.[6] Results stemming from the included studies opting to incorporate all of these key inputs may be seen as more robust and generalizable. Furthermore, combining such studies into a formal meta-analysis may have added valuable economic evidence in support of vaccinating the target population; however, heterogeneity in the economic outcomes reported by the included studies precluded such a design.

In spite of notable differences in clinical outcomes and study design, many inputs were comparable across studies. Both direct medical and indirect costs were considered by each investigation, using reliable sources, and all related costs of vaccination and its administration were considered; however, one exception (Nichol et al.[9]) did exist, and in that case the low value for the

cost of vaccination led to a break-even value for vaccination costs above the values cited by the other studies. Additionally, the impact of moderate adverse events related to vaccination was included by most of the studies; however, the economic impact of these events showed considerable variation.

4.3 Quality of Included Studies

The studies reviewed herein provide distinct assessments of the economics of vaccinating healthy working-age adults. While the included RCTs were well designed and allowed for the analysis of primary data, these studies had limitations. The Bridges et al.[8] study, although providing comparison across influenza seasons and analyses from two perspectives, involved a small sample size with only a limited sensitivity analysis. Similarly, the Nichol et al.[7] 1995 trial was limited by its sample size in addition to other factors: lack of laboratory-confirmed cases, attack rate higher than usual for a working-age population and no sensitivity analysis. Additionally, the Nichol et al.[9] 2003 RPCT was limited by a lack of complete intervention costs as well as its use of febrile illness to gauge influenza incidence; however, the use of such primary data allowed for the analysis of LAIV in a healthy working-age group. Of the three, the study by Bridges et al.[8] is perhaps the most robust, in spite of its shortfalls, providing analysis from two perspectives and including multiple measures of influenza-related health outcomes. Moreover, the multiple-year structure of this particular trial allows for the comparison of influenza vaccination across years where differing annual effects due to the circulating strains or attack rates may be factored into the interpretation of results. Such annual variance in effects suggests that future studies of influenza may be strengthened by incorporating multiple years into the analysis.

Studies using simulation models or decision trees also varied in strengths and limitations. The study by Lee et al.,[11] while strong in its analysis of the combined use of vaccination and antivirals, is limited in several aspects. The most important limitation is that the authors employed a probability of illness that may be considered relatively high for this age group. Additionally, relevant health outcomes such as mortality, hospitalization and outpatient visits were omitted from the analysis. Deaths were similarly omitted from the study by Rothberg and Rose,[12] as were variables included in the sensitivity analysis that resulted in less than a 30% change in incremental cost-effectiveness ratios. Such details may have added value to the analysis regardless of the magnitude of their economic impact. QALYs were further impacted by utility valuations used to measure the quality-of-life estimates that even the authors suggest may be too high.[12] Additionally, the values used to establish vaccination costs in this case were comparatively low. However, elements of both of these studies may lack current applicability as resistance to two of the involved treatments (rimantadine and amantadine) has been observed in circulating strains in recent influenza seasons.[17]

Nichol[10] included all relevant clinical endpoints (mortality, hospitalization and outpatient/emergency room visit) in the analysis, allowing for a more complete assessment as well as the inclusion of the impact of lost earnings on economic outcomes. An added strength of this study is also seen in its robust sensitivity analysis. However, although this was the only included study that showed baseline cost savings in the target population, these results may be misleading. One problem is that the authors reported a vaccine-related reduction in clinical outcomes of 5.5 per 100, yet they used a base-case clinical attack rate of only 5%, suggesting that the base-case values fall outside of the stated range. Additionally, as estimates of reduced worker effectiveness were captured only through employee surveys, this impact of influenza on company performance and profitability is not completely understood. As such, results should be interpreted with caution considering how this parameter was employed in this model.[10]

Similar to Nichol's assessment, Prosser et al.[13] incorporated several clinical endpoints as well as the lifetime impact of lost earnings associated with mortality. However, unlike the other included studies, this study incorporated comparison groups of differing ages and higher risks

against which healthy working-age adults may be evaluated. This study also analysed the cost effectiveness of vaccination at sites other than a physician's office, providing perspective on the impact of alternative sites for vaccination, the results of which have become increasingly important as the landscape of available locations to be vaccinated continues to evolve. Although primary analysis did not include dollars per QALY, this study offers the most robust analysis, of those included in this review, of vaccinating a healthy, working-age population.

In all but one instance (Nichol et al.[7]), sensitivity analysis was performed by the study investigators. In most cases, all variables were included, providing for a stronger analysis of the effects of varied parameter estimates; however, Bridges et al.[8] chose to vary only select variables (costs of lost workdays and vaccination and the rates of ILI), resulting in only limited ability to assess the impact of changes in parameter estimates. All but one of the trials varying each parameter reported complete results of their sensitivity analysis. However, Lee et al.[11] merely reported on the variables to which the model's optimal treatment strategy were more sensitive, including related threshold values. Further, Rothberg and Rose[12] only reported select variables from their sensitivity analysis; therefore, the impact of variation in the remaining parameters on incremental cost effectiveness cannot be assessed.

All results described may need to be revisited in response to the degree by which the working-age population was affected by the recent pandemic influenza. A disproportionate number of adults aged 18–49 years were especially vulnerable to complications of the H1N1 virus circulating in 2009.[1] It is possible that the impact of this particular influenza season may have had larger than normal effects on productivity levels in the country during peak months of the outbreak. In subsequent years, the H1N1 strain has been included in the seasonal influenza vaccine and, as such, additional analysis of our target population is warranted to assess the impact of this form of the vaccine on the working-age population in conjunction with the updated ACIP recommendation.

5. Conclusion

The studies reviewed suggest that vaccinating working-age adults in the US against seasonal influenza is not generally cost saving but may be economically attractive under certain conditions, such as higher illness rates, lower costs of vaccination and higher wage rates. While many of the reviewed studies are of high quality, the lack of definitive measurements for many of the input values means that there is still need for further investigation into this subject.

Acknowledgements

Funding for this project was provided by the Harvard-CDC Joint Initiative in Vaccine Economics. The authors acknowledge the valuable contributions of Drs Carolyn Bridges, Guillermo Herrera, Marie Griffin and Ron Keren who reviewed the presubmission manuscript.

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention or the Department of Health and Human Services.

The authors have no conflicts of interest that are directly relevant to the content of this review.

References

1. Kuehn BM. CDC Advisory committee recommends nearly universal influenza vaccination. JAMA 2010; 303 (12): 1136
2. Fiore AE, Shay DK, Broder K, et al. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009 [published erratum appears in MMWR Recomm Rep 2009 Aug 21; 58 (32): 896-7]. MMWR Recomm Rep 2009 Jul 31; 58 (RR-8): 1-52
3. Bridges CB, Winquist AG, Fukuda K, et al. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2000; 49 (RR-3): 1-38
4. Drummond MF, O'Brien BJ, Stoddart GL, et al. Methods for the economic evaluation of health care programmes. 2nd ed. Oxford: Oxford University Press, 1997
5. US Department of Labor, Bureau of Labor Statistics. Consumer Price Index. 2010 [online]. Available from URL: http://www.bls.gov/cpi/#tables [Accessed 2010 Aug 5]
6. Molinari NAM, Ortega-Sanchez IR, Messonnier ML, et al. The annual impact of seasonal influenza in the US: measuring disease burden and costs. Vaccine 2007; 25: 5086-96
7. Nichol KL, Lind A, Margolis KL, et al. The effectiveness of vaccination against influenza in healthy, working adults. N Engl J Med 1995; 333 (14): 889-93
8. Bridges CB, Thompson WW, Meltzer MI, et al. Effectiveness and cost-benefit of influenza vaccination of healthy

working adults: a randomized controlled trial. JAMA 2000; 284 (13): 1655-63

9. Nichol KL, Mallon KP, Mendelman PM. Cost benefit of influenza vaccination in healthy, working adults: an economic analysis based on the results of a clinical trial of trivalent live attenuated influenza virus vaccine. Vaccine 2003; 21: 2207-17
10. Nichol KL. Cost-benefit analysis of a strategy to vaccinate healthy working adults against influenza. Arch Intern Med 2001; 161: 749-59
11. Lee PY, Matchar DB, Clements DA, et al. Economic analysis of influenza vaccination and antiviral treatment for healthy working adults. Ann Intern Med 2002; 137: 225-31
12. Rothberg MB, Rose DN. Vaccination versus treatment of influenza in working adults: a cost-effectiveness analysis. Am J Med 2005; 118: 68-77
13. Prosser LA, O'Brien MA, Molinari NAM, et al. Non-traditional settings for influenza vaccination of adults. Pharmacoeconomics 2008; 26 (2): 163-78
14. Hammond ML, Ferris AA, Faine S, et al. Effective protection against influenza after vaccination with subunit vaccine. Med J Aust 1978; 1: 301-3
15. Keech M, Scott AJ, Ryan PJ. The impact of influenza an influenza-like illness on productivity and healthcare resource utilization in a working population. Occup Med (Lond) 1998; 48: 85-90
16. Savidan E, Chevat C, Marsh G. Economic evidence of influenza vaccination in children. Health Policy 2008; 86: 142-52
17. Fiore AE, Fry A, Shay D, et al. Antiviral agents for the treatment and chemoprophylaxis of influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2011; 60 (RR01): 1-24

Correspondence: *Justin Gatwood*, University of Michigan College of Pharmacy, 428 Church St, Ann Arbor, MI 48109-1065, USA.
E-mail: gatwood@umich.edu