MAJOR ARTICLE

Cost-Effectiveness of Vaccination versus Treatment of Influenza in Healthy Adolescents and Adults

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At present time, there is uncertainty regarding whether influenza-like illness in healthy adults is best managed by preventive efforts that use the trivalent influenza vaccine, administration of neuraminidase inhibitors at the onset of illness, or recommendation of supportive care alone at the onset of illness. We conducted a cost-effectiveness analysis that examined these 3 strategies for managing influenza-like illness. Vaccination with inactivated trivalent vaccine would save approximately $25 per person while resulting in a net gain of ~3.2 quality-adjusted hours relative to providing treatment with the neuraminidase inhibitor oseltamivir. A quality-adjusted hour is a fraction of a quality-adjusted life-year, which is the equivalent of 1 year lived in perfect health. Treatment with oseltamivir was associated with an incremental cost-effectiveness of approximately $27,619 per quality-adjusted life-year gained relative to providing supportive care. Vaccination is cost-saving relative to providing either treatment with oseltamivir or providing supportive care alone.

Influenza virus infections account for ~30,000 deaths, upward of 200,000 hospitalizations, and more than a million ambulatory care visits and days of lost work in the United States each year [1–4]. However, mortality for adults who do not have diabetes, chronic lung disease, or heart disease is rare, and hospitalization rates are much lower than they are among elderly individuals or persons with chronic disease [4]. Nonetheless, undervaccination of healthy adults almost certainly results in morbidity and mortality when the virus is transmitted from healthy persons to persons who are highly susceptible to influenza and its complications.

In the past, attempts to examine the economic costs and benefits of influenza virus vaccination have been limited to small vaccine trials, which have produced equivocal results [5–9]. The primary limitations of these studies were that the sample sizes were too small to calculate rates of hospitalization; they were conducted in particular geographic regions; and they only collected data during 1–2 seasons. Because the incidence of influenza is highly variable from region to region and from year to year, it is not surprising that some studies have demonstrated savings, whereas others have demonstrated costs associated with vaccination of healthy adults. To date, no comprehensive cost-effectiveness analysis has been conducted on vaccination of healthy adults, in part because of data limitations. Recently, morbidity and mortality data for influenza virus infections have become available, which makes such an analysis possible [4].

In 1999, two neuraminidase inhibitors, oseltamivir and zanamivir, were introduced to international mar-

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Table 1. Assumptions used in deriving parameter estimates and justification.

Assumption	Justification
No deaths would occur among healthy adults infected with influenza virus infection	Few data were available [4]
10% of all patients with influenza-like illness will visit a clinician within 48 h	This assumption was based on expert opinion and tested in a broad sensitivity analysis
95% of clinicians will prescribe oseltamivir during the therapeutic window of 48 h after the onset of symptoms	This assumption was tested in a broad sensitivity analysis
95% of patients will be compliant with oseltamivir	Efficacy data were obtained from randomized controlled trials [10–13]; compliance with medications under real-world conditions is likely to be lower than that observed under experimental conditions
The risk of hospitalization or death caused by influenza will be reduced by 50% among persons taking oseltamivir	The observed reduction in secondary complications among subjects taking oseltamivir in one randomized controlled trial was 50% [1]; a broad sensitivity analysis was conducted on this parameter

kets for use in the management of influenza virus infections [10–13]. In studies published elsewhere, both agents were shown to reduce the duration and severity of influenza infection, and to date, the oral preparation, oseltamivir, has not been associated with serious side effects [10–14]. The Centers for Disease Control and Prevention recommends that persons who are at increased risk for influenza complications, such as elderly individuals, receive the vaccine at the beginning of the influenza season [14]; however, among healthy adults, there is uncertainty regarding whether vaccination with the trivalent influenza vaccine, treatment of influenza-like illness (ILI) with neuraminidase inhibitors, or supportive care alone is the most cost-effective strategy for reducing morbidity and mortality associated with influenza.

Universal vaccination requires administration of the vaccine to persons who otherwise might not develop illness while exposing them to the risks of experiencing minor side effects and rare but serious events, such as Guillain-Barré syndrome [15]. Neuraminidase inhibitors are an attractive alternative to vaccination because they are administered only to persons who develop illness, and like the influenza vaccine, they may decrease antibiotic consumption and secondary complications of influenza. However, neuraminidase inhibitors are considerably more expensive than the influenza vaccine, they attenuate rather than prevent the illness, and they require administration within 48 h after the onset of symptoms [10, 11, 16]. In this study, we examine the costs and effectiveness of vaccination, presumptive treatment with neuraminidase inhibitors, and supportive care (rest, hydration, symptom relief, and medical care as needed) for healthy adults with ILI aged 15–65 years.

METHODS

Overview and definitions. All healthy adults aged 15–65 years residing in the United States in 1997 were entered into a decision-analysis model as a hypothetical cohort. We adhered to the reference case guidelines of the Panel on Cost-Effectiveness in Health and Medicine [17]. The analysis was conducted from the societal perspective and includes all relevant costs except secondary transmission of the influenza virus. In our effectiveness equations, we assumed that no deaths would occur, biasing the analysis in favor of the supportive care option.

"ILI" is defined here as subjectively determined fever or a measured temperature of $\geqslant$37.7°C plus cough or sore throat (the World Health Organization definition) [18]. Although some studies that we included in our analysis used slightly different definitions of ILI, we adjusted the data by means of comparative parameters [9].

ILI is a constellation of upper and lower respiratory conditions; therefore, it is associated with a high incidence rate of illness; although ~40%–50% of the civilian noninstitutionalized population in the United States contracts a disease that meets this symptomatic definition during the course of an influenza season, the incidence rate of influenza virus infections is much lower, averaging <10 cases per 100 persons per year [6, 9–12, 19, 20]. Many of the conditions that meet the technical definition of ILI, however, would probably not be mistaken for influenza infection at a clinical examination. However, some of these conditions may arise as a complication of a recent infection with the influenza virus [11]. In our analysis, all studies (except 1 study in which the incidence of influenza was not measured [5]) were conducted during an influenza season in which the incidence rate of influenza virus infection was <10%.

Decision-analysis model. A decision-analysis model was constructed using DATA, version 3.0 for Macintosh (TreeAge Software), that examined 3 strategies: (1) vaccination of all persons with the inactivated trivalent vaccine each influenza season, (2) empirical treatment of persons developing ILI with oral oseltamivir, 75 mg b.i.d. for 5 days, or (3) provision of supportive care only. All assumptions of the model are listed in table 1. The model was designed to obtain the probabilistically weighted average cost and effectiveness of each strategy

by use of the inputs listed in table 2. Each strategy was associated with a similar pathway of events: (1) the probability of illness, (2) the probability of a medical visit (including the probability of illness secondary to a primary influenza virus infection), (3) the probability of receiving antibiotics for secondary illnesses, (4) the probability of receiving over-the-counter medications, and (5) the probability of hospitalization. In the treatment and vaccination arms, the probability of side effects was also included, as were the costs of each treatment.

Costs. The costs associated with hospitalization caused by influenza virus infection and its complications were obtained from the 1997 Healthcare Cost and Utilization Project–3, a weighted database that includes information about approximately one-half of all hospital discharges in the United States [21]. Because hospital charges may not reflect the true societal costs of hospitalization, charges were converted to costs by use of cost-to-charge ratios derived from the Medical Provider Analysis and Review system of the Health Care Finance Administration [22]. Costs associated with ambulatory medical care were obtained from the medical literature [5, 9]. The cost of syringes preloaded with influenza vaccine, oseltamivir, and over-the-counter medications were obtained by use of average wholesale prices from the *Red Book* and the medical literature [5, 9, 25]. The cost of vaccination included 30 min of patient time ($8.37) and 5 min of time for administration by a registered nurse ($1.70) [26, 27]. We estimated over-the-counter drug consumption and costs by use of weighted mean values from randomized controlled trials published in the medical literature [9, 11].

Transportation use was estimated on the basis of data from the Bureau of the Census [28]. Costs associated with travel to work or school were adjusted for the number of persons carpooling, biking, or walking [28]. Persons who were ill with an ILI were assigned 2.8 days of bed rest [29]; thus, they were not expected to incur costs associated with traveling to work during that time period.

Caregiver support costs were obtained from the medical literature, the Bureau of Labor Statistics, and the Bureau of the Census [26, 27]. Patient time included time spent in transit to a medical clinic or hospital, in addition to the time spent receiving ambulatory care or hospital services. All costs were adjusted to 1997 US dollars.

Table 2. Selected parameters included in the decision-analysis model.

Parameter	Base	High	Low	Source
Cost per patient, 1997 US dollars				
Hospitalization, mean	$5734.00	$7454.00	$4014.00	[21–24]
Guillain-Barré syndrome	$100,800.00	$130,000.00	$70,000.00	[23]
Medical office visit for ILI	$64.39	$84.00	$45.00	[6, 9]
5-Day course of oseltamivir[a]	$49.82	$53.00	$25.48	[25]
Influenza vaccine, administration, and patient time	$12.57	$16.75	$6.99	[26–28]
Over-the-counter medications for ILI	$8.48	$11.03	$5.94	[9, 25]
Caregiving costs for persons with ILI	$53.56	$69.62	$37.49	[29]
Reduced transportation and environmental costs for ILI				
Money saved when bed bound with ILI	$19.49	$28.25	$10.72	[26–28]
Money spent visiting doctor	$6.96	$10.09	$3.83	[26–28]
Probability of				
Development of ILI	0.49	0.50	0.21	[6, 9, 12, 15]
Compliance with oseltamivir	0.95	1	0.5	Assumed
Guillain-Barré syndrome	1×10^{-6}	9×10^{-6}	0.5×10^{-6}	[15]
Hospitalization for influenza[b]	0.00024	0.024	0.00018	[4, 30]
Proportionate improvement, oseltamivir	0.213	0.248	0.18	[10–14]
Physician prescribing oseltamivir within 48 h	0.95	1	0.1	Assumed
Medical visit for ILI, supportive care arm	0.75	0.58	0.91	[6, 9]
Medical visit for ILI, treatment arm	0.695	0.54	0.91	[6, 9, 12]
Medical visit for ILI, vaccination arm	0.38	0.23	0.53	[6, 9]
Medical visit related to side effects[c]	0.01	0.05	0	[10–14, 6, 9]
Health-related quality of life	0.61	0.79	—	[31]

NOTE. ILI, influenza-like illness.

[a] Dosage was 75 mg b.i.d. Cost was deflated to $1997 using average medical inflationary rate, 1994–1997.

[b] Among persons ill with ILI.

[c] The probabilities of side effects from influenza vaccination and oseltamivir were approximately equivalent.

Table 3. Costs, effectiveness, and incremental cost-effectiveness of the 3 interventions studied among 15–65-year-old persons.

Parameter	Total cost	Total effectiveness	Incremental cost[a]	Incremental effectiveness[a]	Incremental cost-effectiveness[b]
Support	$66.39	0.00779	—	—	—
Treatment	$77.99	0.00821	$11.60	0.00049	$27,619
Vaccination	$52.92	0.00853	($25.07)[c]	0.00037	Savings[d]

NOTE. All outcomes occur within 1 year; thus, no discounting is applied. Values are rounded.

[a] The incremental change in cost or effectiveness is calculated by subtracting the cost or effectiveness of an intervention from the cost or effectiveness of the next-most-effective intervention.

[b] The incremental cost-effectiveness ratio is calculated by dividing the incremental cost of an intervention by the incremental effectiveness of that intervention.

[c] Parentheses indicate savings.

[d] It is not possible to calculate a cost-effectiveness ratio for cost-saving interventions.

Probabilities. The mean rate of hospitalization as a result of influenza infection or its complications was obtained from the medical literature [4, 30]. These studies encompass 19 years of data for healthy persons aged 15–65 years. From the medical literature, we obtained the probabilities of the following: (1) side effects from vaccination or oseltamivir [10–14], (2) medical visits in vaccinated and unvaccinated persons [5, 9], (3) Guillain-Barré syndrome [15] resulting from influenza vaccination, and (4) secondary bacterial infections arising as a result of influenza [11]. The efficacy of the vaccine in the prevention of ILI [6, 9] and influenza virus infection [9] was adjusted on the basis of an estimate that the vaccine would be poorly matched to circulating influenza strains approximately once every 10 years [9]. Data obtained from the general population in the United States were adjusted by accounting for the proportion of the population in the United States that was vaccinated in 1997 [32] and the efficacy of the trivalent influenza vaccine [9, 19] so that these rates would reflect those of an unvaccinated cohort.

The range of incidence rates for ILI during an average influenza season were determined by the mean rate from a number of prospective studies [6, 9, 12, 20]. No data were available on the probability of a medical visit for persons treated with oseltamivir. To estimate this probability, we adjusted the rate of ambulatory visits in unvaccinated, untreated persons by reducing the expected number of medical visits by the number of secondary complications averted in persons treated with oseltamivir. The proportionate reduction in the duration of influenza-like symptoms (21.3%) was used to apportion hours of ill time and healthy time among persons treated with oseltamivir [11].

Quality-adjusted life-years. We calculated quality-adjusted life-years (QALYs) under the assumption that no deaths would occur among healthy adults. The Quality of Well-Being (QWB) scale was used to estimate the health-related quality of life (HRQL) score for persons with ILIs [31]. The QWB scale converts data pertaining to mobility, physical activity, and social dimensions of a disease, along with information about the symptoms and problems a disease produces, to an HRQL score. The Years of Healthy Life (YHL) measure was used to assess the baseline health status of persons in the United States [33].

Sensitivity analysis. Baseline parameter estimates and the range of plausible values for each estimate are listed in table 2. All variables were tested for their influence on the model by a multivariate sensitivity ("tornado") analysis. Variables that demonstrated sufficient influence on the rank order of the cost or effectiveness of each intervention were then tested in 1-way and, where appropriate, bivariate sensitivity analyses. All assumptions were tested by use of broad 1-way sensitivity analyses. To test effectiveness parameters, we ran the model with an HRQL score obtained from the Health Utilities Index (HUI) mark 2 and varied the baseline health state of the cohort by means of the YHL measure [33, 34].

We also conducted a Monte Carlo simulation under the assumption that all variables would be triangular in distribution. The triangular distribution is a probability distribution in which the baseline value of a parameter is assigned the highest probability of occurrence and the extreme high and low values of a parameter are assigned the lowest probability of occurrence. The probability of observing a value in between the baseline value and either the high or low value assigned to a variable is linearly interpolated.

RESULTS

Table 3 lists the average cost per person and effectiveness of the 3 interventions under study. The decision-analysis model predicted that the cost of vaccinating persons aged 15–65 years (approximately $53 per person) would be lower than the cost of treatment with oseltamivir (approximately $78 per person) or supportive care (approximately $66 per person) when the incidence of ILI is 49 cases per 100 persons. Vaccinating all persons aged 15–65 years would result in a net gain of ~0.00037 QALYs or 3.2 quality-adjusted hours and savings of approxi-

mately $25 per person relative to providing treatment during an average influenza season.

Vaccinating all persons aged 15–65 years would result in a net gain of ~0.00074 QALYs or 6.5 quality-adjusted hours and savings of approximately $13 per person relative to providing supportive care during an average influenza season (data not shown). Treatment with oseltamivir was associated with an incremental cost-effectiveness ratio of $27,619 per QALY relative to supportive care.

When tested for costs, the model was most sensitive to the following variables, in descending order of sensitivity: incidence of ILI, transportation costs, caregiver costs, the cost of a medical visit in the vaccination arm, and the cost of the influenza vaccine. Vaccination remained the dominant strategy when each of these variables was tested over the range of plausible values of each parameter (table 2).

The incidence of ILI was the major determinant of the predicted cost savings. When the incidence of ILI was greater than ~24.2 cases per 100 persons, vaccination was cost-saving relative to providing only supportive care (figure 1).

The decision model was robust with respect to changes in the plausible values of all variables. On the basis of a 2-way analysis of the incidence of ILI and vaccine efficacy, we estimate that vaccination would only be expected to be associated with costs approximately once every 10 years. None of the assumptions made in the analysis affected the dominance of the vaccination strategy when tested over a broad range of values. When the HUI was substituted for the QWB scale to calculate QALYs, the effectiveness of the supportive-care arm increased by 10%, the treatment arm increased by 8%, and the vaccination strategy increased by 6%. The Monte Carlo analysis predicted that vaccination would be the cost saving in ~75% of all trials; provision of supportive care would be dominant in ~15% of trials.

It is feasible that future generic versions of neuraminidase inhibitors will be significantly less expensive than are current formulations. If a 5-day course of oseltamivir were made available for less than approximately $15.00, it would be a cost-saving intervention relative to supportive care. Vaccination would be slightly less costly than oseltamivir overall, even if this medication were free.

The costs of vaccination in this analysis only included the costs of the influenza vaccine, medical supplies, vaccine administration, and patient time because our recommendations were to promote vaccination in the workplace or as part of a medical visit for reasons unrelated to influenza infection. If all patients were to visit their doctors specifically to receive the influenza vaccine, vaccination would be associated with an incremental cost-effectiveness ratio of $31,081 relative to supportive care.

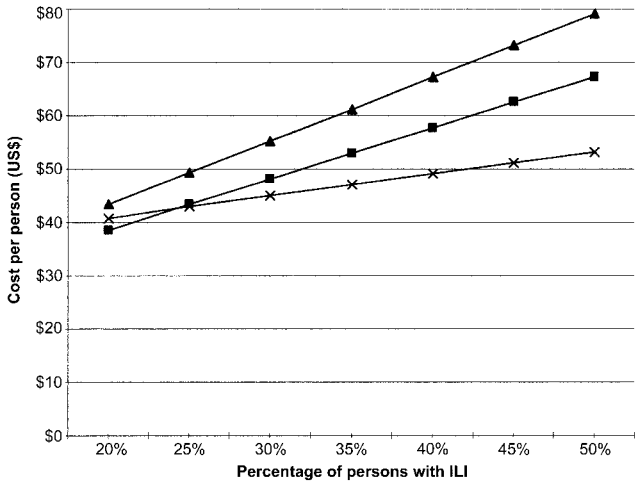

Figure 1. One-way sensitivity analysis of the incidence of influenza-like illness (ILI). As the incidence of ILI increases, the per-person cost of the vaccination arm (×) increases less rapidly than the cost of supportive care (■) or treatment (▲) with oseltamivir, resulting in lower overall costs for vaccination than for the other strategies when the incidence of ILI is >24.2 cases per 100 persons. The base case rate of ILI is 49%.

DISCUSSION

Vaccinating persons aged 15–65 years with the inactivated trivalent influenza vaccine is cost saving relative to treating symptomatic persons with oseltamivir or providing supportive care. Vaccination of all persons in this age group would save approximately $25 and 0.0004 QALYs per person relative to provision of treatment during an average influenza season (table 3). Treating only those persons who developed an ILI with oseltamivir would cost approximately $27,619 per QALY gained relative to supportive care.

Because our initial analysis demonstrated that vaccination was dominant even when tested over a wide range of plausible values in a sensitivity analysis, we chose not to model the possible effects of herd immunity produced by vaccinating all persons aged 15–65 years, neuraminidase inhibitor–resistant influenza viruses, or laboratory testing for the influenza virus. Inclusion of each of these effects would only increase costs in the oseltamivir arm while increasing savings of both dollars and lives with vaccination.

Our study was limited by a number of factors. First, we had difficulty in adjusting data to the World Health Organization definition of ILI [18], which is a constellation of symptoms not consistently defined in the medical literature. Although the use of this symptom-based definition allowed us to improve the model of the diagnosis, treatment, and prevention of influenza infection in the real world, it affected the comparability of the different parameters we used.

We also had difficulty in obtaining a precise incidence rate for ILI in unvaccinated persons. Although the incidence rate

of influenza virus infections varies 5%–27% between different geographic regions and different studies [9, 19, 20, 35], the incidence rates of ILI reported in the medical literature are generally much higher [6–9, 12, 19, 20], because ILI encompasses a broader range of infectious agents. Nonetheless, vaccination remained cost saving, relative to supportive care, provided the incidence rate of ILI was >24 cases per 100 persons, which is well below rates quoted in the medical literature.

No data were available on the efficacy of oseltamivir in reducing the consumption of medical resources or mortality caused by influenza virus infections. We assumed that medical use would be reduced in proportion to reductions in the rate of secondary illness among persons treated with oseltamivir. In a retrospective cohort study of influenza-associated mortality in women [4], 2 excess deaths occurred per 100,000 person-months in healthy subjects; however, this rate was not significantly higher than was the rate observed during the peri-influenza season. Although secondary transmission of the influenza virus from healthy adults to persons at risk for death would likely be reduced by vaccination, we were unable to obtain a reliable estimate of the extent to which this intervention would reduce mortality nationwide. Because the vaccination strategy was found to be dominant and because inclusion of deaths averted in our analysis would only have strengthened these findings, we chose to exclude deaths from the analysis altogether.

Finally, we used the QWB scale to derive the HRQL for persons with ILI. This instrument is based on category scaling measurements—a method that does not technically produce utilities [31]. We chose this instrument rather than the HUI [34] because the health dimensions it incorporates are similar to those produced by ILI. Because the methods used to obtain utilities for the QWB scale differ from those used in other instruments, variation in HRQL values can occur [33]. Substituting the HUI score for the QWB score did not affect the relative dominance of vaccination, because this strategy is considerably more effective than oseltamivir at reducing the total number of days subjects spend with an ILI. However, the use of the HUI score did differentially affect the effectiveness of each intervention under study.

HRQL scores typically assume a value from 0 to 1.0, with 0 being equivalent to death and 1.0 equivalent to perfect health. Although our hypothetical cohort consisted of adults without chronic lung disease, chronic heart disease, or diabetes mellitus, the cohort would not be expected to be in perfect health. The QWB scale was designed to assign a value to a particular disease, and it cannot be used to estimate the overall health of a population. For this reason, we used the YHL measure to estimate the overall health of our cohort for persons who did not develop an ILI and for persons who recover from an ILI.

Cost-effectiveness analyses associated with cost savings are rare and typically include interventions targeted toward high-risk populations, such as pneumococcal vaccination to prevent bacteremia in elderly populations, or presumptive treatment of parasitosis in immigrant populations [36, 37]. Although less cost-effective than vaccination, neuraminidase inhibitors [10–14, 38, 39] may be a cost-effective modality for preventing morbidity and mortality in unvaccinated persons who present to medical practitioners with an ILI. Of the currently available management strategies to address influenza infection in the healthy adult population in the United States, vaccination is the most cost-effective method to decrease health care costs, morbidity, and mortality, and it should be strongly considered for all persons without contraindications to the vaccine.

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