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Economic Analysis of Influenza Vaccination and Antiviral Treatment for Healthy Working Adults

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Background: **Physicians have several treatment options for influenza, including vaccination and various antiviral therapies. However, the optimal influenza prevention and treatment strategy is unknown.**

Objective: **To compare the relative health values of contemporary treatment strategies for influenza in a healthy sample of working adults.**

Design: **Cost–benefit analysis using a decision model.**

Data Sources: **Previously published data.**

Target Population: **Healthy employed adults 18 to 50 years of age.**

Time Horizon: **A complete influenza season.**

Perspective: **Societal.**

Interventions: **Eight treatment options (yes or no) based on the possible combinations of vaccination and antiviral therapy (rimantadine, oseltamivir, or zanamivir or no treatment) should infection develop.**

Outcome Measures: **Cost in U.S. dollars, including the value of symptom relief and medication side effects, which was assigned a monetary value through a conjoint analysis that used a "willingness-to-pay" approach.**

Results: **In the base-case analysis, all strategies for influenza vaccination had a higher net benefit than the nonvaccination strategies. Vaccination and use of rimantadine, the most cost-beneficial strategy, was $30.97 more cost-beneficial than nonvaccination and no use of antiviral medication. The health benefits of most antiviral treatments equaled or exceeded their costs for most scenarios. The choice of the most cost-beneficial antiviral strategy was sensitive to the prevalence of influenza B and to the comparative workdays gained by each antiviral therapy.**

Conclusions: **Vaccination is cost-beneficial in most influenza seasons in healthy working adults. Although the benefits of antiviral therapy for persons with influenza infection appear to justify its cost, head-to-head trials of the various antiviral therapies are needed to determine the optimal treatment strategy.**

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Each year, influenza affects 10% to 20% of the U.S. population (11). In high-risk populations, such as elderly persons, influenza causes up to 20 000 deaths per year (2). Even in young healthy persons, influenza significantly affects direct health care costs, losses in worker productivity, and quality of life (3). In terms of therapy, yearly vaccination can reduce the risk for influenza, and various antiviral medications (for example, amantadine, rimantadine, zanamivir, and oseltamivir) can decrease the duration of illness for a person with influenza. However, yearly vaccination of healthy adults is not absolutely recommended, and it remains unclear whether the benefits of anti-influenza medications justify the costs (4, 5).

We compared the costs and benefits of contemporary preventive and treatment strategies for influenza in a sample of healthy working adults. We conducted our study as a cost–benefit analysis because most effects of influenza in a healthy adult sample (work-days lost and symptoms) are noncatastrophic. Using a decision model, we compared competing strategies by incorporating influenza vaccination versus nonvaccination and antiviral therapy (zanamivir, oseltamivir, rimantadine, and amantadine) for infected patients. This decision model considered the direct costs (for example, medication costs) and indirect costs (for example, lost wages) associated with each treatment strategy. In addition, our model incorporated the patient-determined relative value for relief from influenza symptoms and for avoiding medication side effects. To measure these variables, we used survey data and a conjoint analysis by using a utility valuation approach. Finally, we used sensitivity analysis to identify factors that could affect the optimal strategy. Our work adds to previous studies in considering antiviral strategies for influenza infection.

METHODS

Model Overview

We used a decision tree to model the choices of whether to vaccinate and whether to treat influenza (if influenza infection occurred) with one of several agents (**Figure**). The decision model was constructed for healthy persons 18 to 50 years of age without any significant comorbid conditions. All costs and benefits were framed from a societal perspective, which we defined as the perspective on outcomes of an intervention that accounts for all health effects (harms and benefits) and all costs (regardless of whether a monetary transaction occurs and who pays). We used the following equation to calculate our cost–benefit analysis:

$$\text{net benefit (cost)} = \text{benefits of vaccination and treatment} - \text{costs of vaccination and treatment.}$$

The Appendix, available at www.annals.org, provides the details of the equation and model. In brief, we included in the model eight treatment options—the eight possible

Context

Strategies to decrease the adverse consequences of influenza include vaccination and antiviral therapy. No previous study has compared these two strategies in healthy working adults.

Contribution

In this cost–benefit analysis, vaccination strategies resulted in higher net benefits than strategies that did not include vaccination. The health benefits of most antiviral treatments equaled or surpassed their costs.

Clinical Implications

Vaccinating healthy working adults against influenza is an economically attractive strategy for preventing the adverse consequences of influenza.

Antiviral treatment for persons infected with influenza also saves money, but head-to-head comparisons of the available therapies are needed to define the most cost-effective regimen.

–The Editors

combinations of influenza vaccination before infection (yes or no) and antiviral therapy if infection developed (using rimantadine, oseltamivir, or zanamivir or no treatment). We initially considered amantadine therapy as a possible treatment option, but because amantadine has a higher incidence of side effects than rimantadine and amantadine was less efficacious, amantadine was dominated by rimantadine in all subsequent analyses and was excluded. Because we were considering a healthy young population, we did not assume that vaccination or antiviral therapy would affect mortality or provide any long-term health benefits. Although these assumptions are conservative, they are consistent with the results of previous trials in healthy young persons (3, 6). We programmed the model using DATA software, version 3.5 (Treeage Software, Williamstown, Massachusetts).

Probabilities

Table 1 shows the value estimates used in the base case and the ranges evaluated in our sensitivity analysis. For a healthy adult, the probability of contracting influenza during an influenza season has been estimated to be 15% (range, 1% to 35%) (6–9). Vaccine efficacy for preventing influenza infection was estimated to be 68% (range, 50% to 86%) (6). Because rimantadine is effective only against influenza A and because oseltamivir and zanamivir are each effective against influenza A and influenza B, the prevalence of influenza B is important in determining the optimal antiviral therapy. The baseline prevalence of influenza B among influenza strains in a given year was assumed to be 16.3% (range, 1% to 86%) on the basis of the average yearly rate for prevalence of influenza in the United States over the past 10 years (Unpublished data). In terms of side effects, we considered the probability that rimantadine caused side effects of the central nervous system (characterized as dizziness, nervousness, and anxiety) in 2% of patients and gastrointestinal side effects (characterized as nausea) in 1% of patients (2, 3). For oseltamivir therapy, the probability of gastrointestinal side effects (characterized as nausea) was considered to be 9% (29). Because significant

Figure. **Decision tree showing the strategies for influenza prevention and treatment.**

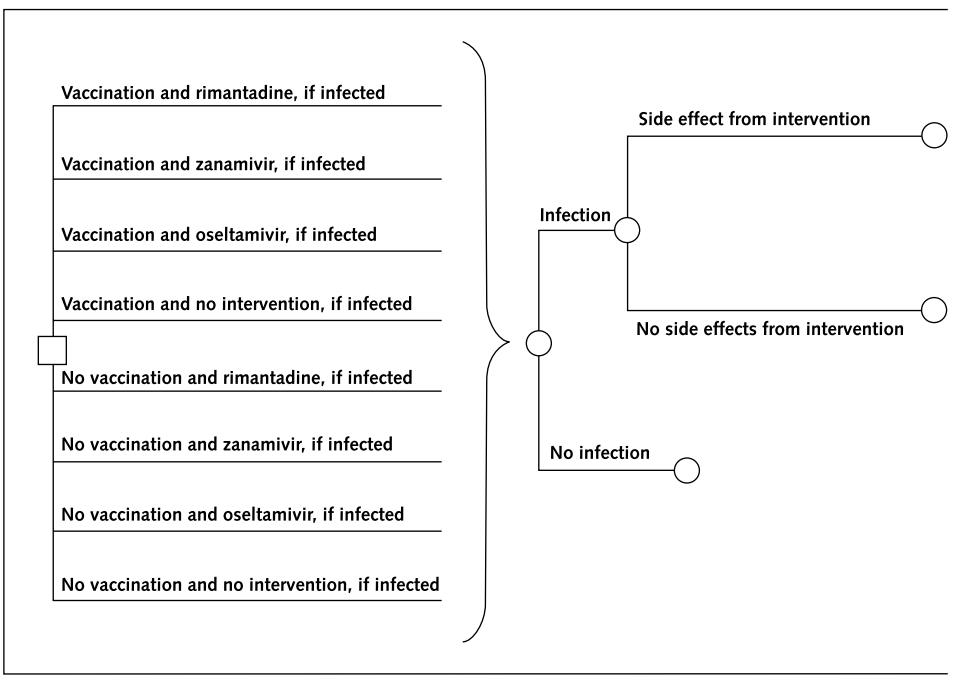

Table 1. **Base-Case Values and Ranges***

Variable	Base-Case Value (Range)	Reference
Probability of influenza illness, %	15 (1–35)	6–10
Vaccine efficacy, %	68 (50–86)	3, 6
Probability of side effects of the central nervous system from use of rimantadine, %	2 (0–5)	11, 12
Probability of gastrointestinal side effects from use of rimantadine, %	1 (0–5)	11, 12
Probability of gastrointestinal side effects from use of oseltamivir, %	9 (5–15)	14
Prevalence of influenza B virus, %	16 (1–86)	Unpublished data
Probability of using antibiotic for influenza infection, %	17 (0–40)	14
Probability of using antibiotic and antiviral therapy for influenza infection, %	11 (0–40)	14
Cost of vaccination, $†	10.41 (5–20)	6, 15
Opportunity cost of time lost for vaccination, $‡	8.88 (0–35)	16
Daily wage, $§	142.10 (80–250)	16
Cost of physician visit, $	27.00 (15–40)	17, 18
Cost of rimantadine therapy, $	17.50 (10–25)	19
Cost of zanamivir therapy, $	47.50 (30–60)	20
Cost of oseltamivir therapy, $	57.22 (40–70)	20
Cost for use of one course of antibiotics, $‖	17.50 (10.00–35.00)	6
Work time lost for one episode of influenza without treatment, *workdays*	2.8 (0.5–7)	21, 22
Work time gained from use of rimantadine, *workdays*¶	0.5 (0.1–1.0)	
Work time gained from use of zanamivir, *workdays*	0.5 (0.1–1.0)	13, 23–25
Work time gained from use of oseltamivir, *workdays*	0.5 (0.1–1.0)	13, 23, 26, 27
Amount willing to pay to avoid side effects of the central nervous system, $	56.39 (0–600)	
Amount willing to pay to avoid gastrointestinal side effects, $	61.79 (0–600)	
Amount willing to pay for 1 day of symptom relief, $	15.49 (0–600)	
Duration of symptoms, *d*	5 (3–7)	11
Duration of symptom relief from use of rimantadine, *d*	1.27 (0.77–1.77)	11
Duration of symptom relief from use of zanamivir, *d*	1 (0.6–1.3)	13, 23–25
Duration of symptom relief from use of oseltamivir, *d*	1 (0.6–1.3)	13, 23, 26, 27

* All costs are in 2001 U.S. dollars and were calculated by using the 2001 medical cost and wage index (28).
† The cost of vaccination (the vaccine and administration) was estimated to be $10.80 on the basis of data from a previous trial (6).
‡ To calculate the opportunity cost of time for vaccination, the time required for vaccination was assumed to be 0.5 hour (range, 0 to 1 hour), and employees' time was valued at $17.77 per hour.
§ The average daily wage for a U.S. worker, assuming a 40-hour work week and 50 work weeks per year, is $142.10 (16).
‖ The cost of one course of antibiotic therapy was assumed to be $7.50, which was the cost of antibiotic therapy for code 487.1 of the International Classification of Diseases, 9th revision ("influenza, not otherwise specified") (6).
¶ Number of workdays saved by using rimantadine was assumed to be the same as that for the neuraminidase inhibitors because the days of symptom relief were the same for both therapies.

side effects rarely occur with use of influenza vaccine or zanamivir, the probabilities for these variables were not included in the base-case model (3, 6, 9, 13). Finally, on the basis of a previous study (14), we assumed that 17% of patients who developed influenza infection would receive antibiotic therapy (at a drug cost of $17.50) (12). This figure was reduced to 11% in infected patients who received antiviral medication, based on data from a previous study (14).

Costs

All costs and benefits are expressed in 2001 U.S. dollars. We calculated these dollar figures on the basis of 2001 medical cost and wage index data (28). The cost of vaccination, including the cost of administration, was $10.41 (15); a 5-day course of rimantadine therapy was $17.50 (19), and 5-day courses of zanamivir and oseltamivir therapies were $47.50 and $57.22, respectively (30, 31). The cost of a physician visit was assumed to be $17.00 (Current Procedural Terminology code 99201, office or other outpatient visit) (range, $15 to $40) (17, 18). Patients were assumed to incur these costs when seeking treatment with any of the antiviral therapies. Two recent trials reached different conclusions on whether vaccination saves the cost of physician visits. Because the vaccines come from different years, the vaccines in these two trials had nonmatching antigens and differed in terms of efficacy (6, 9). To be conservative about the benefits of vaccination, we assumed that vaccination did not save costs from physician visits.

For antiviral therapy, we initially assumed that medication-related side effects would not require additional physician office visits. We tested this assumption by modeling a physician visit for each medication side effect experienced and found that results on optimal strategy were unchanged. No trial has demonstrated that vaccination or antiviral therapy decreases hospitalization rates for influenza-related illness (3, 6)

Benefits

For each episode of influenza infection, an average of 2.8 workdays are lost (21, 22). Wages gained by avoiding influenza because of vaccination therefore equaled 2.8 days times an average daily wage of $142.10 (16), or $397.88. On the basis of a recent meta-analysis of published trials (11), zanamivir and oseltamivir were each assumed to relieve an average of 1.0 day of symptoms, while rimantadine was assumed to relieve 1.27 days of symptoms. It is also unknown whether antiviral therapies reduce the severity of symptoms. To be conservative in our estimates of antiviral therapy effectiveness, we assumed that the antiviral medi-

Table 2. **Base-Case Results***

Strategy	Value Compared with That of No Vaccination and No Intervention, $
Vaccination and use of rimantadine, if infected	30.97
Vaccination and use of zanamivir, if infected	30.13
Vaccination and nonintervention, if infected	29.50
Vaccination and use of oseltamivir, if infected	29.39
Nonvaccination and use of rimantadine, if infected	4.61
Nonvaccination and use of zanamivir, if infected	1.97
Nonvaccination and nonintervention, if infected (base case)	–
Nonvaccination and use of oseltamivir, if infected	−0.032

* All strategies were compared with the base case.

cations did not reduce symptom severity. Clinical trials have also demonstrated that with use of zanamivir or oseltamivir, adults returned to normal activity an average of 0.5 day earlier compared with no prescription drug use (13). Thus, because no data exist on the number of workdays gained with antiviral therapy, we assumed a gain of 0.5 workday. Trial data on the number of workdays saved because of rimantadine use were also unavailable. Given that rimantadine was at least as effective as the neuraminidase inhibitors in relieving symptoms, we assumed the same number of workdays saved (0.5 days) in our base-case analysis. We tested these assumptions of workdays gained in a sensitivity analysis.

Value of Symptom Relief and Avoided Side Effects

We assessed the value to infected patients of symptom relief and avoided side effects from medication use by considering their "willingness to pay." To determine a patient's willingness to pay for a day of symptom relief and for avoided drug side effects, we used patient survey data, which we analyzed using a conjoint analysis approach. Conjoint analysis involves three interrelated assumptions: 1) Each treatment is a bundle of potential attributes; 2) each person has a unique utility or value for each attribute level that is assumed to be unaffected by the levels of the other attributes present; and 3) combining the different utilities for different attributes provides an individual's overall utility or preference for a specific treatment (32).

In a conjoint analysis, participants are presented with a set of hypothetical scenarios consisting of different attribute levels for each treatment option. (The survey that we used is available at www.annals.org [**Appendix Figure**]). Each person is asked to state the percentage chance that he or she would choose a particular option. The tradeoffs between the costs and benefits of various treatment options are then calculated by using regression analysis. (Details of our regression analysis are available in the Appendix at www.annals.org)

For the current analysis, we surveyed 210 patients seeking primary care at a family practice clinic in North Carolina. These patients were surveyed to determine their willingness to pay for a day of relief from influenza symptoms, for avoidance of nausea as a side effect of medication, and for avoided dizziness as a side effect of medication.

Sensitivity Analysis

We performed a one-way sensitivity analysis for each variable using the plausible ranges shown in **Table 1**. In probabilistic sensitivity analyses, we varied all variables simultaneously over their plausible ranges. Each variable was entered as a triangular distribution (centered on the baseline value) with end points set at the extremes of the probable ranges. Values for each variable were then randomly selected during each iteration of the model. The model was then run for 1000 iterations to determine how often each strategy was considered the optimal or most cost-beneficial strategy. We tested other probability distributions; however, the results of the sensitivity analysis were not changed substantially (data not shown).

Role of the Funding Sources

The funding sources had no role in the collection analysis, or interpretation of the data or in the decision to submit the paper for publication.

RESULTS

Decision Model

Table 2 shows the base-case values of competing strategies relative to the strategy of no vaccination and no treatment if infection occurred. All strategies for influenza vaccination were found to have a higher net benefit than strategies without vaccination. Likewise, the benefit of antiviral strategies (used in combination with vaccination or alone) equaled or exceeded their costs in our base-case simulation. Among antiviral medications, rimantadine was most cost-beneficial, although it caused slightly more side effects. Therefore, the therapeutic strategy of vaccination and use of rimantadine if infection occurred was the most cost-beneficial strategy based on the values of the decision

Table 3. **Results of Sensitivity Analysis**

Variable	Base Value	Threshold	Alternate Favored Strategy
Probability of influenza infection, %	15	<6.3	Nonvaccination and use of rimantadine
Work time lost for one episode of untreated influenza, *workdays*	2.8	<0.98	Nonvaccination and use of rimantadine
Prevalence of influenza B virus, %	16.33	>35	Vaccination and use of zanamivir
Work time gained from use of rimantadine, *workdays*	0.5	<0.35	Vaccination and use of zanamivir
Work time gained from use of zanamivir, *workdays*	0.5	>0.62	Vaccination and use of zanamivir
Work time gained from use of oseltamivir, *workdays*	0.5	>0.73	Vaccination and use of oseltamivir

model. When compared with no vaccination and no intervention if infection occurred, this strategy had a net benefit of $30.97. Analysis of the patient survey data revealed that a patient's willingness to pay for a day of relief from influenza was $15.49; from nausea, $61.79, and from dizziness, $56.39.

Sensitivity Analysis

The model was not sensitive to most variables over the plausible ranges shown in **Table 1**. **Table 3** shows the factors to which the model's optimal treatment strategy were sensitive. For the decision of whether to vaccinate, the model was sensitive to the prevalence of influenza in a given year and the workdays affected by influenza-related illness. Specifically, if the probability of influenza infection was less than 6.3%, not vaccinating was more cost-beneficial than vaccinating. Likewise, if less than 0.98 workdays was lost because of influenza infection, not vaccinating was more cost-beneficial. Of note, vaccine efficacy did not affect the optimal antiviral strategy over the plausible ranges; in fact, the threshold value at which vaccine was no longer cost-beneficial was 29%, which is less than half of our estimate for vaccine efficacy. Similarly, the cost of the antiviral agents did not affect the optimal antiviral strategy.

Two variables were found to affect the optimal antiviral treatment strategy. First, if the prevalence of influenza B during a season was greater than 35% (as it was in two of the past 10 U.S. seasons [Unpublished data]), then zanamivir was the optimal antiviral strategy. Second, the model was highly sensitive to assumptions about the relative effectiveness of each antiviral drug for improving worker productivity. If zanamivir therapy increased the number of saved workdays by 0.12 day more than rimantadine, then zanamivir was the favored antiviral therapy. Similarly, if oseltamivir saved 0.23 more workdays than rimantadine, then it was the dominant antiviral therapy, despite its higher initial cost. Willingness to pay for relief from symptoms or to avoid side effects did not affect the results over the ranges of the sensitivity analysis.

The model's sensitivity to the assumption of workdays was particularly important. Previous randomized trials of antiviral therapies have not determined whether symptom relief from antiviral therapy actually translates into workdays gained. At one extreme, we tested whether antiviral therapy could be cost-beneficial solely on the basis of the patients' willingness to pay for symptom relief. Even if no workdays were gained from antiviral therapy, vaccination and rimantadine would still be the most cost-beneficial strategy if patients were willing to pay more than $40 for a day of symptom relief.

Because the incidence of nausea and dizziness is higher with rimantadine than with zanamivir, we also tested whether patients' valuation of side effects would alter the decision pattern between rimantadine and the newer neuraminidase inhibitors. Given the base-case differences in drug cost and the relative rarity of side effects, even when the probability of side effects of rimantadine was increased to its plausible maximum, patients would have to be willing to pay more than $279.50 to avoid an episode of dizziness and more than $284.90 to avoid an episode of nausea before zanamivir would become the favored therapy.

Patients with non–influenza-related upper respiratory infections may also receive antivirals. Because data are lacking on the false-positive rates for antiviral treatments in patients who do not actually have influenza, we examined this possibility with our sensitivity analysis. We found that more than 40% of patients treated with antiviral therapies would have to develop noninfluenza infections for antiviral therapies not to be considered cost-beneficial.

Finally, using a probabilistic sensitivity analysis, we simultaneously varied the base-case values of all costs and probabilities (**Table 4**). Among 1000 simulations, strategies that included vaccination were favored over nonvaccination strategies in 95% of the iterations. Vaccination combined with antiviral therapy was the optimal strategy in 79% of the iterations. Likewise, in cases of influenza infection, strategies that included an antiviral agent (rimantadine, zanamivir, or oseltamivir) were found to be optimal (compared with no antiviral therapy) in 85% of the iterations. Under no circumstances were nonvaccination and nonintervention the preferred strategy. Vaccination combined with rimantadine was found to be the dominant strategy in 35% of the iterations, followed by vaccination combined with zanamivir in 31% of the iterations. The probabilistic sensitivity analysis was simulated by using normal distribution, triangular distribution, and uniform distribution of the variables, without any difference in the results.

Table 4. **Results of Probabilistic Sensitivity Analysis**

Strategy	Proportion of Iterations in Which the Strategy Was Optimal, %
Vaccination and use of rimantadine	35
Vaccination and use of zanamivir	31
Vaccination and use of oseltamivir	14
Vaccination and nonintervention	15
Nonvaccination and use of rimantadine	3
Nonvaccination and use of zanamivir	1
Nonvaccination and use of oseltamivir	1
Nonvaccination and nonintervention	0

DISCUSSION

The relative values of vaccination in conjunction with different treatment strategies in healthy working adults have not been previously compared. In our analysis, in almost all scenarios, vaccination proved to have a higher net benefit than nonvaccination. The relative values of the various antiviral strategies also covered their costs and were determined primarily by the number of workdays gained. Without the indirect benefit of workdays saved, strategies that used vaccination and antiviral therapy would not be

cost-beneficial. Among the antivirals, rimantadine showed a slight advantage over the neuraminidase therapies.

Our conclusions regarding vaccination are consistent with the results of one of the two previous randomized, controlled trials of influenza vaccination (6, 9). Nichol and colleagues (9) determined a cost savings of $46.85 per vaccination in a study sample with an infection rate of 35%, which is at the upper limits of the sensitivity analysis. In contrast, Bridges and colleagues (6) found a net cost of $65.59 and $11.17 per vaccination over two seasons. However, two key differences between our study and that of Bridges and colleagues explain the conflicting findings. First, in the study by Bridges and colleagues, patients' willingness to pay for symptom relief or avoidance of side effects was not considered. Second, the study by Bridges and colleagues found that an episode of influenza resulted in only 0.5 workday lost per episode (33). If we used this rate in our model, we also would have concluded that vaccination is not cost-beneficial. Finally, of note, neither of these studies considered antiviral therapies for patients who had influenza.

In an economic evaluation of the most effective preventive strategy for influenza in British army personnel (34), which did not evaluate antiviral medications, vaccination was determined to be better than nonvaccination. Our study expands on this finding by including findings on antiviral medications as treatment strategies, the indirect cost of lost wages, and patients' willingness to pay for symptom relief and for avoidance of side effects.

Sensitivity analysis regarding vaccination also revealed that the decision to vaccinate could shift depending on the probability of influenza and the number of workdays lost per episode. These factors are not readily predictable at the beginning of an influenza season. To the extent that our base case represents average prevalence data and the results are relatively robust, vaccination is probably the optimal strategy among all patients, not just in high-risk groups, such as elderly persons.

With regard to antiviral therapy, our results suggest that rimantadine may be underutilized relative to the newer, more expensive neuraminidase inhibitors. Although rimantadine causes side effects slightly more frequently than these newer agents, the side effects are less severe in healthy adults than in elderly persons. In particular, the fear of rimantadine's side effects of the central nervous system were based in the elderly population and were possibly the result of decreased renal clearance (11). Our analysis demonstrates that if rimantadine was assumed to cause dizziness at more than double its documented rate, patients would need to be willing to pay nearly $300 to avoid dizziness before rimantadine would no longer be the favored antiviral strategy. In our conjoint analysis survey, we found that patients were willing to pay only approximately 20% of this amount ($56). The potential for influenza resistance to rimantadine has been documented (35, 36), but the clinical importance of such resistance is unknown. Furthermore, to be conservative about the effects of antiviral therapy, we assumed that these interventions did not prevent hospitalizations due to influenza. Finally, rare cases of bronchospasm have been reported with use of zanamivir in persons with asthma (37).

Although a strategy including rimantadine was found to be superior to a strategy including zanamivir, probabilistic sensitivity analysis revealed that rimantadine and zanamivir were almost interchangeable, given that the difference in workdays saved was minimal. Changes in the prices of the neuraminidase inhibitors, particularly decreases in price as more drugs enter the market, could shift the optimal antiviral strategy. Results of our sensitivity analysis indicated that even if no workdays were to be gained by using these drugs, use of the evaluated medications would still be cost-beneficial if the willingness to pay for 1 day of symptom relief is increased approximately threefold for rimantadine or fivefold for zanamivir.

Limitations

Our study has several limitations. First, data in the literature are limited on the efficacy of antivirals in terms of workdays saved. Thus, we assumed that the variable of "return to normal activity" reported in previous studies was a proxy for workdays saved. Small differences in workdays saved will shift the optimal antiviral strategy. Second, willingness-to-pay variables are affected by various factors not directly addressed here, such as income. Therefore, in our sensitivity analysis, we varied the ranges for these variables by more than 10 times their base values. Finally, given the high cost and rare use at the population level for healthy working adults, we did not consider postexposure prophylaxis with antivirals.

Conclusions

Our results indicate that vaccination in a variety of settings is cost-beneficial in most influenza seasons for a healthy working population 18 to 50 years of age. Although universal vaccination would be more cost-beneficial from a societal perspective, individual insurers would not reap the benefits of indirect medical benefits and would probably need government subsidization to promote universal vaccination. Rimantadine is the optimal strategy in predominantly influenza A seasons, but neuraminidase inhibitors may be interchangeable in terms of economic benefit. Given the limited data regarding the efficacy of antivirals in workdays saved, head-to-head comparisons of these antivirals are needed to determine the most cost-beneficial therapy. Any such study must be powered to detect small differences in workdays saved because small shifts in efficacy will determine the most cost-beneficial strategy. Such a study should also include vaccination, given the range of workdays gained in previous studies. Our model highlights a research agenda to measure the number of workdays saved by using antiviral therapies to determine the optimal treatment strategy.

APPENDIX

Technical Information

The decision model is based on eight separate strategies (**Figure**).

The probabilities at the infection node are as follows:

If patient receives vaccination: probability of influenza × (1 − vaccine efficacy).

If vaccination is not done: probability of influenza.

The probabilities at the nodes for side effects are based on the side effects of each antiviral agent examined.

For zanamivir: no probabilities for side effects of the central nervous system or gastrointestinal system.

For oseltamivir: probabilities used for side effects of the central nervous system or gastrointestinal system.

For rimantadine: probabilities used for side effects of the central nervous system.

The overall equation for the costs and benefits of the vaccination groups is as follows:

Costs = cost of antiviral therapy (if used) + cost of physician visit (if patient develops infection) + willingness to pay to avoid central nervous system effects (if antiviral therapy is used and the patient experiences side effects of the central nervous system) + willingness to pay to avoid nausea (if antiviral therapy is used and the patient experiences nausea from the medication) + workdays lost × wage + workdays lost because of influenza symptoms × willingness to pay to avoid influenza symptoms + probable antibiotic use if antiviral therapy used (if an antiviral is used) × cost of antibiotic therapy + probable antibiotic use if no antiviral used (if no antiviral is used) × cost of antibiotic therapy

Benefits = workdays gained from using antiviral therapy (if used) × wage + symptom days relieved by antiviral medication (if used) × willingness to pay to avoid influenza symptoms × (1 − prevalence of influenza B) (if rimantadine used)

The overall equation to calculate the net benefit (cost) at each node was as follows:

Net benefit (cost) = benefits of vaccination and treatment − costs of vaccination and treatment

Each branch of the decision tree was multiplied by the appropriate probabilities, and net benefit (cost) was calculated for each node. The values for each branch were rolled back to determine the optimal influenza prevention and treatment strategy.

A one-way sensitivity analysis was conducted by varying the values of each variable over their appropriate range, and the decision tree was rolled back to determine the optimal strategy in each of the sensitivity analyses. If varying these variables caused any shift in the optimal strategy, the threshold value at which this occurred was noted.

Probabilistic sensitivity analysis was conducted by first assigning each variable a probability distribution with end points set at the extreme ends of the data ranges. Normal distributions, triangular distributions, and uniform distributions were all tested for each variable. A Monte Carlo simulation with 1000 iterations was run, in which each variable was randomly assigned to a value on the basis of these distributions, and the tree was rolled back in each iteration, showing the most cost-beneficial strategy. The percentage of iterations in which each strategy was most cost-beneficial is shown in **Table 4**.

Conjoint Analysis

Outcomes in the decision model were valued on the basis of the results of a conjoint analysis, which was based on results of a survey of 210 respondents. Conjoint analysis is a stated preference technique designed to establish the effect of individual attributes in the overall utility of a good or service (38). This method of utility measurement has also been used in the medical literature to assess preferences in several areas, including preferences for scoliosis treatment, miscarriage management, female sterilization, and critical care decision making (39–42). We performed a conjoint analysis because the symptoms of influenza do not involve catastrophic events, such as hospitalization or death, and this method is more accurate than other utility methods, such as the time-trade-off or standard gamble technique, for measuring patients' values of noncatastrophic events. Furthermore, in performing a cost–benefit analysis, we needed to transform all willingness-to-pay measures into dollars rather than another measure of utility, such as quality-adjusted life-years.

In this case, the objective of the conjoint analysis was to measure the value of a day of symptom relief to patients and the value of avoiding side effects of medications. Every patient visiting a North Carolina family practice over 5 days was asked to participate in the survey. Twenty-seven patients declined for unspecified reasons, and 229 patients agreed to participate. Five patient surveys were discarded because the patients indicated that they had never experienced influenza or a severe upper respiratory infection. An additional 14 surveys were discarded because the respondents had been hospitalized in the past 6 months or reported having diabetes mellitus, heart problems, kidney problems, asthma, or other respiratory conditions. In total, we calculated the surveys completed by 210 respondents (mean age, 38 years; 60% female; average income, $40 000).

Patients provided demographic information and read a scenario in which they were asked to imagine that they had contracted "the flu." An oral medication was hypothetically made available that reduced the duration of flu-related illness by 1, 2, or 5 days (average duration, 5 days). Respondents were told that they could take an over-the-counter medication for relief of minor symptoms.

Each patient was presented with scenarios varying the days of flu relieved (1, 2, or 5 days), the price of the oral medication (free, $10, or $50), and side effects experienced (none, nausea, and dizziness). They were asked to choose the likelihood of taking each medication on a scale of 0 (won't take) to 10 (will take). There were 27 (3^3) total possible scenarios if all three levels of each attribute were presented. A balanced orthogonal fractional factorial design reduced the number of scenarios to 9 (43). The 9 levels were designed such that each attribute is statistically independent of the others. This results in zero multicolinearity in the dependent variables, which minimizes the expected variance in the estimates.

A mixed-effects regression model (using SAS PROC

MIXED software, SAS Institute, Inc., Cary, North Carolina) was used to estimate patients' value of days of symptom relief and avoided medication-related side effects. It is assumed that the multiple responses from an individual participant are correlated, while responses across participants are assumed to be independent. To account for this clustering within each participant, a mixed-effects regression model was used to obtain estimates of patients' value of days of symptom relief and side effects experienced. Each participant was treated as a random effect, while all other factors were treated as fixed effects. The percentage chance (the patient's likelihood on a scale of 0 to 10) of taking the medication served as the dependent variable. The price ($0, $10, or $50) and days of symptom relief (1, 2, or 5 days) were modeled as linear variables, and the side effects (none; nausea; or dizziness, nervousness, or anxiety) and other demographic variables were modeled as dummy variables.

Individuals' value (in dollars) of days of flu relieved and avoiding side effects were calculated with a discrete bid contingent valuation method (44). This method uses patients' directly stated preferences and values through "bidding" to calculate their willingness to pay. It is called "contingent" valuation because people are asked to state their willingness to pay, contingent on a specific hypothetical scenario and description. For our calculation, we used the following equation (which was included in the SAS PROC MIXED software package):

$$\text{prob} = b_1X_1 + b_2X_2 + b_3X_3 + \ldots + b_nX_n + b'(\text{PRICE}),$$

in which PRICE was the bid price and each b was an estimated regression coefficient. To determine the effect of each factor on a person's willingness to pay, the base probability was set to 0.5 (the value for which the person is as likely to pay as not to pay) and the equation was calculated to determine the PRICE. The result was:

$$\text{PRICE} = -[(0.5/b') + (b_1/b')X_1 + (b_2/b')X_2 + (b_3/b')X_3 + \ldots + (b_n/b')X_n]$$

The dollar value of a unit change in each factor X_i was simply the ratio (b_i/b'). For dichotomous variables (for example, nausea present or absent), this was the individual's estimated "willingness to pay" to avoid nausea as a treatment side effect. For continuous variables (for example, days of symptoms), this corresponded to the patient's willingness to pay to avoid a single day of symptoms. The results of the regression analysis were as follows. The regression coefficient ($\pm$SE) was 0.2892 ± 0.01602 for willingness to pay to avoid an episode of nausea, 0.2639 ± 0.01602 for willingness to pay to avoid an episode of central nervous system effects, 0.07247 ± 0.00385 for willingness to pay to avoid 1 day of influenza, and 0.00468 ± 0.0003 for willingness to pay for $1 (price) ($P < 0.001$ for all variables). This was transformed into a willingness to pay to avoid 1 day of influenza of $15.49; of nausea, $61.79; and of central nervous system effects, $56.39.

Interactions were not tested for because we used a main-effects orthogonal array. This is because the main effects can be estimated independent of each other, but the interactions between these main effects cannot be estimated. We chose to use this fractional design, which would be less time-consuming than other designs, because we were mindful of the limited time that respondents had to complete the survey and, thus, feared that a longer survey could compromise the reliability of the responses.

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