

Management of Influenza in Adults Older than 65 Years of Age: Cost-Effectiveness of Rapid Testing and Antiviral Therapy

Michael B. Rothberg, MD, MPH; Sandra Bellantonio, MD; and David N. Rose, MD

Background: Although antiviral therapy is cost-effective in adults, its cost-effectiveness in older adults has not been studied.

Objective: To determine the cost-effectiveness of influenza testing and treatment strategies for older adults.

Design: Cost-utility decision model.

Data Sources: Clinical trials of antiviral drugs and epidemiologic data.

Target Population: Noninstitutionalized adults older than 65 years of age with influenza-like illness.

Time Horizon: Lifetime.

Perspective: Societal.

Interventions: Rapid diagnostic testing or empirical therapy with antiviral drugs.

Outcome Measures: Cost per quality-adjusted life-year (QALY) saved.

Results of Base-Case Analysis: Compared with no intervention, empirically treating an unvaccinated 75-year-old patient with amantadine increased life expectancy by 0.0014 QALY at a cost of

\$1.57, a cost-effectiveness ratio of \$1129 per QALY saved. Compared with amantadine, rapid diagnostic testing followed by treatment with oseltamivir cost \$5025 per QALY saved and empirical treatment with oseltamivir cost \$10 296 per QALY saved. Testing and treatment strategies were less cost-effective if the patient was vaccinated, ranging from \$2483 per QALY saved with amantadine to \$70 300 per QALY saved with oseltamivir.

Results of Sensitivity Analysis: The decision was sensitive to the probability of influenza, the efficacy of oseltamivir in preventing hospitalizations, and hospitalization and case-fatality rates. The decision was not sensitive to the probability or severity of medication side effects, the quality of life for influenza illness or hospitalization, the efficacy of antiviral therapy in shortening influenza illness, or the rapid diagnostic test characteristics.

Conclusions: For unvaccinated or high-risk vaccinated patients during the influenza season, empirical oseltamivir treatment is cost-effective. For other patients, rapid diagnostic testing followed by treatment with oseltamivir is cost-effective. Empirical amantadine treatment offers a low-cost alternative if patients cannot afford oseltamivir.

Ann Intern Med. 2003;139:321-329.

For author affiliations, see end of text.

www.annals.org

Influenza virus infection occurs in yearly epidemics, causing an estimated 20 000 deaths and more than 100 000 hospitalizations annually in the United States; a disproportionate number of deaths and hospitalizations occur among older adults (1, 2). Because annual influenza vaccination is both effective and inexpensive, it has been recommended for all persons older than 50 years of age (1). Antiviral drugs for influenza infection have been available for more than 35 years (3), but their use in older adults has been primarily reserved for prophylaxis in nonvaccinated persons during influenza outbreaks.

Two classes of antiviral drugs are available for treating influenza illness. The older drugs, amantadine and rimantadine, decrease the duration of illness in healthy individuals by approximately 1 day (3). Although amantadine costs only \$2 for a 5-day course, its use has been limited by a lack of efficacy against influenza type B; frequent side effects, especially in older adults; and the rapid development of viral resistance (4). The recently released neuraminidase inhibitors, zanamivir and oseltamivir, are effective against both influenza types and reduce the duration of influenza symptoms in average-risk patients by approximately 1 day (5–10) and in high-risk and older patients by 2.5 days (10, 11). In addition, both drugs reduce the incidence of complications requiring antibiotics (7, 10, 12) and may prevent hospitalization (13). Side effects and the emergence of drug resistance are uncommon (14). How-

ever, these newer agents are expensive, ranging from \$48 to \$60 for 5 days of therapy.

To be effective, therapy with all antiviral drugs must be started within 48 hours of the development of symptoms. While the drugs are effective only against influenza, treating physicians must keep in mind that most influenza-like illness is caused by respiratory viruses other than influenza. Moreover, the probability of influenza infection varies by season, location, and the patient's vaccination status. Although rapid office tests are now available, they are less accurate than traditional viral culture and add to the cost of diagnosis.

Antiviral therapy has been shown to be cost-effective in younger adults by decreasing work loss due to influenza illness (15). The cost-effectiveness in older adults, however, is more dependent on decreasing morbidity and mortality. Because no randomized trial has been large enough to estimate the true effect of antiviral therapy on hospitalizations, we constructed a computer model to compare the cost-effectiveness of various testing and treatment strategies for older adults under various assumptions about the effect of antiviral therapy.

METHODS

Decision Analytic Model

We constructed a decision tree (Figure 1) by using Decision Maker 7.07 (Pratt Medical Group, Boston, Mas-

Context

Drugs to treat influenza are cost-effective in adults younger than 65 years of age, but the cost-effectiveness of these drugs for people older than 65 years is unknown.

Contribution

For unvaccinated persons older than 65 years of age with influenza-like illness, empirical treatment with amantadine cost \$1129 per quality-adjusted life-year (QALY), treatment with oseltamivir after rapid diagnostic testing cost \$5025 per QALY, and empirical treatment with oseltamivir cost \$10 296 per QALY. The cost-effectiveness of all strategies was less favorable for vaccinated patients but was always \$70 300 or less per QALY.

Implications

Antiviral drugs are cost-effective for patients older than 65 years of age who develop influenza-like illness. Physicians should choose amantadine or oseltamivir, empirically or after rapid diagnostic testing, after considering patients' vaccination status, comorbidity level, and ability to pay for the drugs.

—The Editors

sachusetts) to compare 9 strategies: 1) no antiviral therapy; 2–5) empirical treatment with amantadine, rimantadine, oseltamivir, or zanamivir; and 6–9) rapid diagnostic testing followed by treatment with each of the 4 antiviral

drugs. We assumed that therapy with all drugs would be initiated within 48 hours of symptom onset and continued for 5 days at doses recommended by the manufacturers.

The model considers prevalence of influenza for non-institutionalized older adults presenting with influenza-like illness (defined as acute onset of fever and cough during influenza season); sensitivity and specificity of rapid diagnostic testing; and the following adverse events: antiviral side effects, influenza complications requiring antibiotics, emergency department visits, hospitalizations, and death. Influenza infection is divided into types A and B, which we assumed to be equally severe. We assumed that only neuraminidase inhibitors would be effective against influenza B. Outcomes were quality-adjusted life-years (QALYs), costs, and cost per QALY saved.

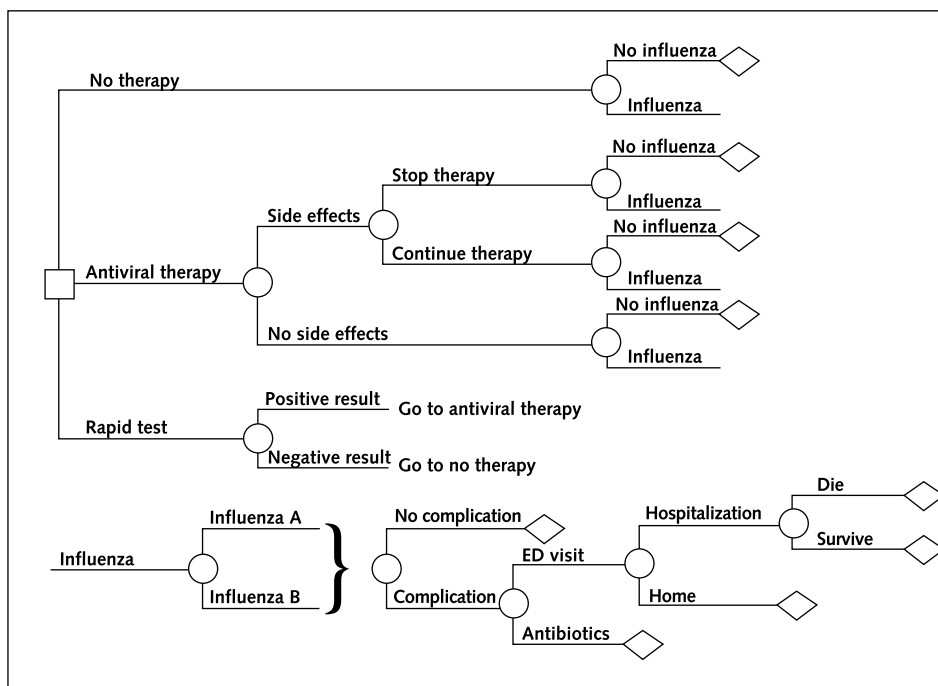
Data and Assumptions

Table 1 lists baseline values for all variables.

Probability of Influenza and Complications

Our base-case patient presents during influenza season, at which time patients with influenza-like illness have a 35% likelihood of having influenza on the basis of diagnosis by a primary care physician (17). We tested other scenarios in the sensitivity analysis. When influenza is known to be circulating regionally, the probability of influenza increases to 70% to 87% (16, 18, 19). During the peri-influenza season (typically October, November, March, and April), the probability decreases to 10% or less (22). For vaccinated patients, who are less likely to have

Figure 1. Decision model treating influenza-like illness in older adults.



Decision node (square), chance events (circles), and terminal nodes (diamonds) are shown. The actual model contains four antiviral therapy branches, one for each antiviral drug. ED = emergency department.

Table 1. Baseline Values for the Decision Model and Ranges Used in Sensitivity Analysis*

Variable	Value at Baseline	Sensitivity Range	Reference
Influenza			
Influenza in patient presenting with acute onset fever and cough	0.35	0.05 to 0.87	7, 16–21
Influenza B, given influenza	0.11	0 to 0.80	22
Death from influenza if hospitalized	0.10	0.05 to 0.15	2, 23
Complication requiring antibiotics	0.27	0.10 to 0.34	10, 11, 21
Hospitalization			
Low risk†	0.044		24
Intermediate risk†	0.098		
High risk†	0.235		
Length of influenza illness, <i>d</i>	7.5		10, 11
Length of hospitalization, <i>d</i>	5.4	4.0 to 7.0	25
Ratio of emergency department visits to hospitalizations	1.74		25
Rapid influenza test characteristics			
Sensitivity	0.73	0.67 to 0.81	Manufacturer's insert
Specificity	0.96	0.93 to 0.99	Manufacturer's insert
Antiviral drugs			
Shortens illness duration, <i>h</i>			
Amantadine	60	24 to 72	26
Rimantadine	60	24 to 72	Assumed
Oseltamivir	60	24 to 72	Assumed
Zanamivir	60	24 to 72	10, 11
Probability of side effects			
Amantadine	0.19	0 to 0.49	27
Rimantadine	0.02	0 to 0.12	27
Oseltamivir	0.10	0.075 to 0.11	5, 7, 20, 28
Zanamivir	0	0 to 0.10	6, 10, 29
Efficacy against complications requiring antibiotics			
Amantadine	0	0 to 0.45	No data
Rimantadine	0	0 to 0.45	No data
Oseltamivir	0.33	0 to 0.45	7, 20
Zanamivir	0.52	0.01 to 0.67	10, 11
Using zanamivir Diskhaler correctly	0.5	0 to 1	30
Vaccine efficacy			
vs. influenza	0.58	0.30 to 0.70	31, 32
vs. complications requiring antibiotics	0.32	0.29 to 0.40	Estimate
vs. hospitalization	0.32	0.29 to 0.40	24
vs. death	0.50	0.44 to 0.56	24
Utility‡			
Influenza	−0.883	−1.0 to 0	33
Hospitalization	−0.983	−1.0 to 0	Estimate
Side effects	−0.23	−1.0 to 0	Estimate
Costs, \$			
Drugs, full treatment course			
Amantadine	1.57		34
Rimantadine	20.40		34
Oseltamivir	59.54		34
Zanamivir	48.02		34
Azithromycin	41.84		34
Amoxicillin	5.10		34
Rapid diagnostic test (QuickVue§)	18	5 to 25	List price
Moderate-complexity office visit	46		35
Emergency department visit	214		25
Hospitalization	4082		25

* All values represent probabilities unless otherwise specified.

† High-risk patients have a baseline diagnosis of heart or lung disease; intermediate-risk patients have a baseline diagnosis of diabetes, renal disease, rheumatologic disease, or dementia or stroke, without underlying heart or lung disease; and low-risk patients have none of these diagnoses.

‡ Negative numbers denote a reduction in quality of life for each day in that health state on a scale of 0, representing no quality reduction, to −1.0, for complete loss of quality.

§ Quidel Corp., San Diego, California.

influenza infection, we decreased the positive predictive value of influenza symptoms by using the formula $Pv = Po \times (1 - e)/(1 - Po \times e)$, where *Pv* is the positive predictive value in vaccinated patients, *Po* is the positive predictive value in unvaccinated patients, and *e* is the efficacy of the vaccine.

The proportion of influenza infections caused by in-

fluenza B viruses varies from year to year and throughout the influenza season. In 2001–2002, our base season, approximately 11% of influenza specimens were type B, but in some weeks, influenza B accounted for more than 80% of influenza isolates (22).

In studies of high-risk patients, defined as having baseline heart or lung disease, approximately one quarter de-

velop complications that require antibiotics (10, 11, 21). Hospitalization occurs in 4.4% of cases in healthy older adults (24); among high-risk older adults, the rate may be 5 times higher (24). Nonhospitalized patients often are confined to bed, and nearly three quarters have impairments in activities of daily living (21).

Vaccination

Vaccination decreases both the probability of contracting influenza and the severity of illness. Efficacy varies from year to year and depends on the degree of match between the vaccine and circulating strains of virus. The vaccine has been shown to decrease hospitalization by one third and mortality by half in high-, medium- and low-risk patients (24). As a result, vaccinated patients have less to gain from antiviral therapy. For this reason, we analyzed vaccinated and unvaccinated patients separately.

Testing and Treatment

We modeled the rapid test Quickvue (Quidel Corp., San Diego, California) because it seems to be the easiest and fastest to use (36). The manufacturer provided test characteristics. We assumed specimens would be collected by using nasal or nasopharyngeal swabs.

Treatment data on older adults are limited. All anti-influenza drugs shorten the duration of influenza illness in healthy volunteers, and zanamivir and oseltamivir decrease the incidence of complications requiring antibiotics (7, 10, 12). Zanamivir was even more effective in high-risk patients (11). No randomized trial was sufficiently powered to detect a difference in hospitalizations or mortality. One observational study showed a statistically significant decrease in mortality (0% versus 12.9%) among nursing home patients treated with amantadine compared with no therapy (26), and another study showed a statistically significant decrease in serious complications, hospitalizations, and deaths among nursing home patients receiving oseltamivir compared with no therapy (13). From this, we deduced that antiviral therapy may prevent hospitalization. Extrapolating from the randomized trials, we estimated that oseltamivir would prevent 33% of hospitalizations, which is proportional to its effect on complications requiring antibiotics. Given the lack of trial data, we assumed that amantadine and rimantadine would not prevent hospitalization or death.

All drugs are available in oral forms except zanamivir, which comes as a Diskhaler. Loading and administering the medication require several steps. One study reported that after 15 minutes of instruction, 50% of older adult patients could not successfully load the device (30). We tested this assumption in the sensitivity analysis.

Probability of Side Effects

Potential side effects of amantadine in older adults include mental status change, orthostatic hypotension, gas-

trointestinal disturbances, and congestive heart failure. Doses need to be adjusted for renal insufficiency. Rimantadine, which is metabolized in the liver, causes fewer central nervous system side effects than amantadine (27, 37). Oseltamivir can cause nausea and vomiting (7). Zanamivir has not been associated with adverse events during clinical trials (6, 10, 29), but it is not recommended for patients with underlying airway disease (38). Because no treatment trials have been conducted in older adults, we modeled side effects from studies of nursing home prophylaxis (27). We estimated that adverse effects would last for 2 days on average and that half of all patients experiencing side effects would stop treatment without therapeutic benefit.

Utilities and Costs

We made quality-of-life adjustments for influenza illness on the basis of data collected from elderly patients by using the EuroQOL instrument (33). Short-term morbidity is expressed on a scale from 0, indicating no effect on quality of life, to -1, indicating a complete loss of quality for each day of illness. In the sensitivity analysis, we tested the full range for each possible health state.

We used a societal perspective in keeping with the recommendations of the Panel on Cost-Effectiveness in Health and Medicine (39). Thus, we considered direct medical costs, including physician office visits, diagnostic tests, medications, and hospitalizations. We assumed that patients would not be employed, and thus, we did not include lost wages. Physician fees were based on a moderate-complexity office visit for an established patient (35). We used the retail price provided from the manufacturer for the rapid diagnostic test. Medication costs were average wholesale prices. Hospitalization costs were based on geriatric patients hospitalized for influenza at 75 hospitals (25). All costs were updated to 2001 U.S. dollars by using the medical care component of the Consumer Price Index (40).

Sensitivity Analysis

Because the value of some variables is uncertain and others vary between patients, we conducted 1-, 2-, and 3-way sensitivity analyses, varying the values throughout the range listed in **Table 1** to evaluate the impact on cost and effectiveness. We also conducted *n*-way probabilistic sensitivity analysis. All variables, except cost, season, risk and vaccination status, and efficacy of amantadine and rimantadine, were entered as probability distributions based on the 95% CIs. We then performed 1000 Monte Carlo simulations. For each iteration, new variable values were randomly selected from within each probability distribution and the associated costs and quality-adjusted life expectancy were calculated.

RESULTS

Base-Case Analysis

We began by considering a healthy, unvaccinated 75-year-old patient with influenza-like illness presenting to a

Table 2. Costs, Average Life Expectancy, and Incremental Cost-Effectiveness of Influenza Strategies for an Unvaccinated 75-Year-Old Patient Presenting with Influenza-Like Illness during Influenza Season*

Strategy	Total Costs	Incremental Costs†	QALE	Incremental QALE‡	Cost-Effectiveness Ratio§
		\$		y	\$/QALY saved
No antiviral therapy	118.86	—	9.9783	—	—
Empirical amantadine	120.43	1.57	9.9797	0.0014	1129
Test, amantadine	137.35	16.92	9.9794	-0.0003	Dominated
Test, zanamivir	137.72	17.29	9.982	0.0021	Extended dominance¶
Test, oseltamivir	138.41	17.98	9.9833	0.0033	5025
Empirical rimantadine	139.26	0.85	9.9801	-0.0032	Dominated
Test, rimantadine	143.19	4.78	9.9796	-0.0037	Dominated
Empirical zanamivir	147.94	9.53	9.9833	4.4×10^{-5}	Extended dominance¶
Empirical oseltamivir	155.56	17.15	9.9849	0.0017	10 296

* QALE = quality-adjusted life expectancy; QALY = quality-adjusted life-year.
 † Represents the difference between the strategy and the next best nondominated strategy.
 ‡ Represents the difference between the strategy and the next best nondominated strategy.
 § The difference in cost divided by the difference in QALE for each strategy compared with the next best nondominated strategy.
 || A dominated strategy costs more and is less effective than another available strategy.
 ¶| Extended dominance applies to strategies that are not cost-effective because another available strategy provides more QALYs at a lower cost per QALY.

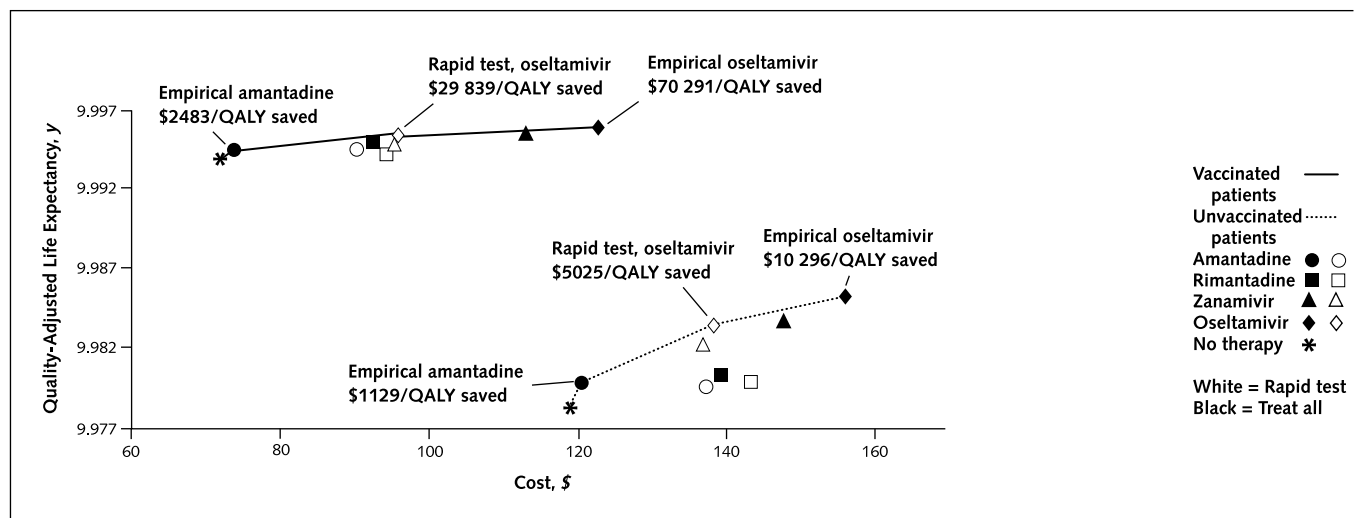
primary care practice during influenza season. Empirical treatment with any anti-influenza drug improved quality-adjusted life expectancy, but oseltamivir was most effective (Table 2). Zanamivir was less effective because of the assumption that some patients would have trouble loading the device properly and would not get a full treatment effect. Amantadine and rimantadine were the least effective of the treatment strategies because of their lack of activity against influenza B and the assumption that neither would prevent hospitalizations. Testing strategies were less effective than empirical treatment because of the low sensitivity of the test.

Achieving better quality-adjusted life expectancy increased cost. Compared with no intervention, treatment

with amantadine increased life expectancy by 0.0014 QALY at a cost of \$1.57, a cost-effectiveness ratio of \$1129 per QALY saved. Compared with amantadine, rapid diagnostic testing followed by treatment with oseltamivir added 0.0033 QALY, at a cost-effectiveness ratio of \$5025 per QALY saved. Empirical treatment with oseltamivir provided the longest life expectancy, with a cost-effectiveness ratio of \$10 296 per QALY saved.

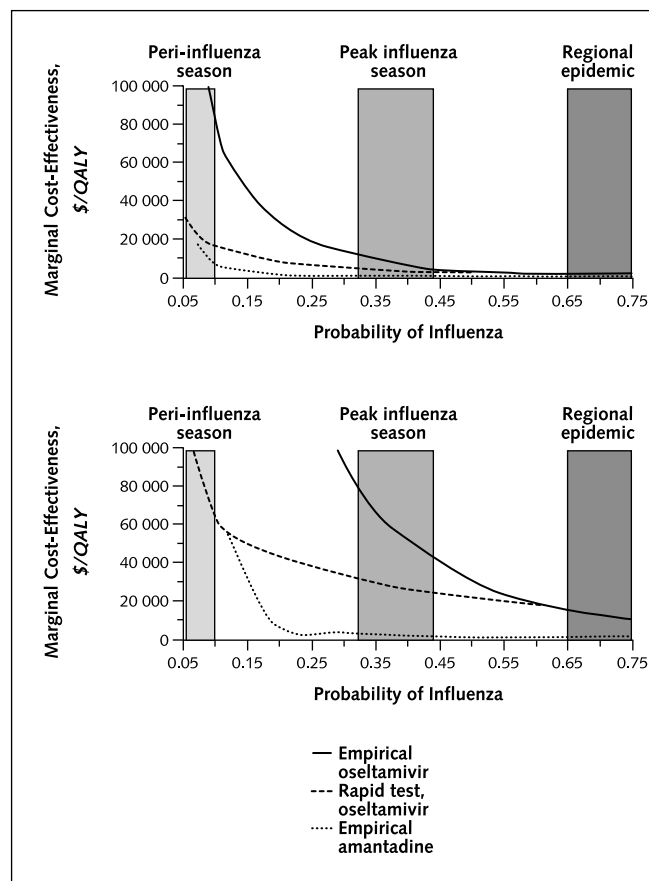
Vaccinated older adults are less likely to be hospitalized or to die of influenza but are only slightly less likely to have influenza symptoms, which are mostly caused by non-influenza viruses. As a result, empirical treatment of influenza symptoms was very expensive relative to the benefits provided. Empirical treatment with oseltamivir still pro-

Figure 2. Incremental cost-effectiveness of testing and treatment strategies for a 75-year-old patient with influenza-like illness.



The testing strategies begin by testing all patients; those whose test results are positive are treated with the drug shown. The two curves represent vaccinated and unvaccinated patients. The lines represent the efficiency frontiers. The slope of the line between two strategies represents the marginal cost-effectiveness of one in relation to the other. Strategies below the line are dominated (that is, more expensive and less effective than one of the strategies on the frontier). QALY = quality-adjusted life-year.

Figure 3. The cost-effectiveness of antiviral therapy or testing as a function of the probability of influenza.



The curves represent the marginal cost-effectiveness of each strategy compared with the next best strategy for unvaccinated (*top*) and vaccinated (*bottom*) patients. The graphs are divided into three zones representing different probabilities of influenza: peri-influenza season, peak season, and regional epidemic. QALY = quality-adjusted life-year.

vided the longest life expectancy but at a cost of \$70 300 per QALY saved. Regardless of the treatment, vaccinated patients lived longer and incurred fewer expenses than did nonvaccinated patients (Figure 2).

Sensitivity Analysis

We varied all the parameters through the ranges presented in Table 1. Only vaccination status, the probability that the patient has influenza, the patient's risk for hospitalization, and the efficacy of oseltamivir in preventing hospitalizations affected the choice of treatment. The model was insensitive to the probability, severity, or duration of side effects; the decrease in quality of life for influenza or hospitalization; the frequency of sinusitis or pneumonia not leading to hospitalization; the efficacy of antiviral therapy in shortening influenza illness; and the sensitivity, specificity, or cost of the rapid diagnostic test.

Probability of Influenza Infection

As the probability of influenza increases, the cost-effectiveness of empirical treatment with oseltamivir im-

proves relative to the testing strategy (Figure 3). Assuming a willingness to pay of \$50 000 per QALY saved, empirical treatment with oseltamivir would be cost-effective for unvaccinated patients at a probability of influenza greater than 14% and testing is preferred at probabilities between 5% and 14%. For vaccinated patients, empirical treatment and testing are cost-effective if the probability of influenza exceeds 41% and 16%, respectively, and no therapy is cost-effective when the probability of influenza falls below 10%.

Effect of Antiviral Therapy on Influenza Complications

In our base-case analysis, we assumed that oseltamivir decreases hospitalization and mortality rates and amantadine does not. If both drugs decrease hospitalizations, then the only advantage of oseltamivir over amantadine is its activity against influenza B and better side effect profile. In that case, oseltamivir's cost-effectiveness worsens to \$85 000 per QALY saved relative to amantadine. Similarly, if oseltamivir does not decrease hospitalizations, then empirical treatment with oseltamivir costs \$334 000 per QALY saved relative to amantadine. In both cases, as the prevalence of influenza B increases, the cost-effectiveness of oseltamivir improves.

Empirical treatment with oseltamivir is most cost-effective when the probability of influenza and hospitalization is high. Figure 4 shows the optimal strategy at different seasons for low-, intermediate-, and high-risk patients. We define the optimal strategy as that which yields the most QALYs at a marginal cost-effectiveness ratio at or below \$50 000 per QALY saved. Empirical treatment with oseltamivir is the optimal strategy for all high-risk patients at any season and for every patient during regional epidemics.

Results of Probabilistic Sensitivity Analysis

We performed probabilistic sensitivity analysis for a low-risk, unvaccinated patient during peak influenza season. The 25th, 50th, and 75th percentiles were \$1047, \$1143, and \$1248 per QALY saved, respectively, for empirical therapy with amantadine relative to no antiviral therapy; \$4465, \$5018, and \$5579 per QALY saved, respectively, for rapid diagnostic testing followed by treatment with oseltamivir relative to empirical treatment with amantadine; and \$9510, \$11 007, and \$12 934 per QALY saved, respectively, for empirical treatment with oseltamivir relative to rapid diagnostic testing. Empirical treatment with zanamivir was the most effective therapy only 2.2% of the time and was dominated by other strategies 79% of the time. Treatment with rimantadine was dominated 100% of the time.

DISCUSSION

This cost-effectiveness analysis demonstrates that community-based older adults benefit from antiviral therapy through an improvement in quality-adjusted life expectancy, if they begin treatment within 48 hours of influ-

Figure 4. Optimal influenza therapy based on risk, season, and vaccination status.

		Peri-Influenza Season (<10%)	Peak Season (33%–44%)	Regional Epidemic (70%–87%)
Risk for Hospitalization	High (24%)	Empirical oseltamivir	Empirical oseltamivir*	Empirical oseltamivir†
	Intermediate (10%)	Unvaccinated patients: Empirical oseltamivir Vaccinated patients: Test, oseltamivir	Empirical oseltamivir	Empirical oseltamivir*
	Low (4%)	Unvaccinated patients: Test, oseltamivir Vaccinated patients: No antiviral therapy	Unvaccinated patients: Empirical oseltamivir Vaccinated patients: Test, oseltamivir	Empirical oseltamivir

The strategy providing the most quality-adjusted life-years at a marginal cost-effectiveness at or below \$50 000 per quality-adjusted life-year saved. The percentages at the top of the figure are probabilities of influenza infection based on timing of presentation. Influenza season varies from year to year. Peak season is generally from December through February in the northern hemisphere; peri-influenza season months include October, November, March, and April; and “regional epidemic” denotes an area where influenza has recently been reported to be widespread. * Cost-saving in unvaccinated patients; † Cost-saving in all patients.

enza-like illness. The benefit comes at a cost. Under most circumstances, antiviral therapy is reasonably cost-effective and within the range of other widely accepted interventions for older adults, such as cholesterol reduction in patients with diabetes (41) or screening mammography (42). The optimal strategy, however, depends on the patient’s vaccination status, the probability that he or she has influenza, and the risk for hospitalization (Figure 4). Empirical treatment with oseltamivir is most cost-effective when the probability of influenza or hospitalization is high. Rapid diagnostic testing followed by oseltamivir treatment, although less effective than empirical treatment, is cost-effective for low-risk patients and vaccinated patients, especially during the peri-influenza season, when influenza is unlikely and empirical treatment is very expensive. Withholding antiviral therapy is appropriate only for low-risk, vaccinated patients during the peri-influenza season.

Earlier cost-effectiveness analyses have focused on young, healthy adults because most of the antiviral therapy trials were conducted in this population (15, 43, 44). Most studies found that antiviral therapy was either cost-effective or cost-saving compared with no intervention, especially when time lost from work was considered. Among young adults, hospitalization or death from influenza are rare events and contribute little to the consideration of therapy.

On the other hand, hospitalization rates in older adults may be 10 to 20 times those of persons younger than 65 years of age, whereas work loss among older adults would be rare. We found that the cost-effectiveness of the neuraminidase inhibitors was predicated on their ability to decrease hospitalizations, as seen in observational studies, something that has yet to be shown in randomized trials. If, in fact, they do not prevent hospitalization, antiviral use would be hard to justify from a cost-effectiveness standpoint. Amantadine, on the other hand, is so inexpensive that its therapeutic use is cost-effective regardless of whether it prevents hospitalization.

Although amantadine is the least expensive anti-influenza drug, its use in older adults may be limited by its side effect profile, specifically its central nervous system side effects. One study of nursing home patients receiving amantadine prophylaxis found that 41% experienced side effects, of which 22% were severe (45). When used as treatment, however, amantadine needs to be administered for only 3 to 5 days, and the incidence of side effects under those circumstances is probably lower. Moreover, even assuming a rate of side effects as high as 49%, amantadine is still cost-effective and may be the only alternative for low-income adults without prescription drug benefits. In frail patients, especially those with congestive heart failure or

elevated serum creatinine levels, amantadine should be avoided. Rimantadine, which is moderately expensive and has fewer side effects than amantadine but is less effective than the neuraminidase inhibitors, was not cost-effective under any circumstances.

Although no head-to-head trials have been conducted, zanamivir seems to be at least as efficacious as oseltamivir in shortening influenza illness and preventing complications that require antibiotics. Moreover, zanamivir is better tolerated and less expensive than oseltamivir. However, trials have included few individuals older than 65 years of age. A study of hospitalized patients reported that after 15 minutes of instruction, 50% of patients in this age group could not correctly load the zanamivir Diskhaler (30). Other studies have not found this (46). If patients can use the medication correctly, zanamivir is more cost-effective than oseltamivir.

Our study has several limitations. To date, there is very little information about the effectiveness of anti-influenza drugs in older adults. There are no comparative trials, and the effects of treatment on hospitalization are unknown. We believe our assumption that lower rates of bacterial complications will translate into averted hospitalizations is reasonable. Given the magnitude of the problem, randomized trials should be conducted to quantify the effect. In planning future research, our model could be used to project the effect size needed for therapy to be cost-effective. Better data are also needed about the economic impact of influenza on older adults, including medical care and indirect costs to family members providing care at home.

Strategies for preventing influenza morbidity in older adults have mostly concentrated on vaccination. Although our results validate this approach, fewer than two thirds of persons older than 65 years of age are vaccinated annually (1). Recommendations on the use of antiviral therapy have been limited (1, 46); none have considered the cost-effectiveness of antiviral drugs, the role of rapid diagnostic tests, or the importance of vaccination status.

Although future randomized trials may offer more compelling evidence of the cost-effectiveness of these medications, prudent use of them now should decrease morbidity and perhaps mortality. Our model offers a rational approach for testing and treatment based on the probability of disease, underlying illness, and willingness to pay. Higher-risk patients and those more likely to have influenza will benefit most from empirical treatment with a neuraminidase inhibitor. Vaccinated low-risk persons should be tested before receiving a neuraminidase inhibitor. Finally, when ability to pay is low, empirical treatment with amantadine offers a low-cost alternative to the newer antiviral medications.

From Baystate Medical Center, Springfield, Massachusetts; and Tufts University School of Medicine, Boston, Massachusetts.

Potential Financial Conflicts of Interest: None disclosed.

Requests for Single Reprints: Michael Rothberg, MD, MPH, Division of General Medicine and Geriatrics, Baystate Medical Center, 759 Chestnut Street, Springfield, MA 01199; e-mail, Michael.Rothberg@bhs.org.

Current author addresses and author contributions are available at www.annals.org.

References

- Bridges CB, Fukuda K, Uyeki TM, Cox NJ, Singleton JA. Prevention and control of influenza. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2002;51:1-31. [PMID: 12002171]
- Simonsen L, Fukuda K, Schonberger LB, Cox NJ. The impact of influenza epidemics on hospitalizations. *J Infect Dis*. 2000;181:831-7. [PMID: 10720501]
- Jefferson T, Demicheli V, Rivetti D, Deeks J. Cochrane reviews and systematic reviews of economic evaluations. Amantadine and rimantadine in the prevention and treatment of influenza. *Pharmacoeconomics*. 1999;16 Suppl 1:85-9. [PMID: 10623381]
- Wenzel RP. Expanding the treatment options for influenza [Editorial]. *JAMA*. 2000;283:1057-9. [PMID: 10697068]
- Hayden FG, Atmar RL, Schilling M, Johnson C, Poretz D, Paar D, et al. Use of the selective oral neuraminidase inhibitor oseltamivir to prevent influenza. *N Engl J Med*. 1999;341:1336-43. [PMID: 10536125]
- Hayden FG, Osterhaus AD, Treanor JJ, Fleming DM, Aoki FY, Nicholson KG, et al. Efficacy and safety of the neuraminidase inhibitor zanamivir in the treatment of influenza virus infections. GG167 Influenza Study Group. *N Engl J Med*. 1997;337:874-80. [PMID: 9302301]
- Treanor JJ, Hayden FG, Vrooman PS, Barbarash R, Bettis R, Riff D, et al. Efficacy and safety of the oral neuraminidase inhibitor oseltamivir in treating acute influenza: a randomized controlled trial. U.S. Oral Neuraminidase Study Group. *JAMA*. 2000;283:1016-24. [PMID: 10697061]
- Monto AS, Fleming DM, Henry D, de Groot R, Makela M, Klein T, et al. Efficacy and safety of the neuraminidase inhibitor zanamivir in the treatment of influenza A and B virus infections. *J Infect Dis*. 1999;180:254-61. [PMID: 10395837]
- Matsumoto K, Ogawa N, Nerome K, Numazaki Y, Kawakami Y, Shirato K, et al. Safety and efficacy of the neuraminidase inhibitor zanamivir in treating influenza virus infection in adults: results from Japan. GG167 Group. *Antivir Ther*. 1999;4:61-8. [PMID: 10682150]
- Randomised trial of efficacy and safety of inhaled zanamivir in treatment of influenza A and B virus infections. The MIST (Management of Influenza in the Southern Hemisphere Trialists) Study Group. *Lancet*. 1998;352:1877-81. [PMID: 9863784]
- Lalezari J, Champion K, Keene O, Silagy C. Zanamivir for the treatment of influenza A and B infection in high-risk patients: a pooled analysis of randomized controlled trials. *Arch Intern Med*. 2001;161:212-7. [PMID: 11176734]
- Kaiser L, Keene ON, Hammond JM, Elliott M, Hayden FG. Impact of zanamivir on antibiotic use for respiratory events following acute influenza in adolescents and adults. *Arch Intern Med*. 2000;160:3234-40. [PMID: 11088083]
- Bowles SK, Lee W, Simor AE, Vearncombe M, Loeb M, Tamblyn S, et al. Use of oseltamivir during influenza outbreaks in Ontario nursing homes, 1999-2000. *J Am Geriatr Soc*. 2002;50:608-16. [PMID: 11982659]
- Two neuraminidase inhibitors for treatment of influenza. *Med Lett Drugs Ther*. 1999;41:91-3. [PMID: 10535051]
- Lee PY, Matchar DB, Clements DA, Huber J, Hamilton JD, Peterson ED. Economic analysis of influenza vaccination and antiviral treatment for healthy working adults. *Ann Intern Med*. 2002;137:225-31. [PMID: 12186512]
- Zambon M, Hays J, Webster A, Newman R, Keene O. Diagnosis of influenza in the community: relationship of clinical diagnosis to confirmed virological, serologic, or molecular detection of influenza. *Arch Intern Med*. 2001;161:2116-22. [PMID: 11570941]

17. Govaert TM, Dinant GJ, Aretz K, Knottnerus JA. The predictive value of influenza symptomatology in elderly people. *Fam Pract*. 1998;15:16-22. [PMID: 9527293]
18. Boivin G, Hardy I, Tellier G, Maziade J. Predicting influenza infections during epidemics with use of a clinical case definition. *Clin Infect Dis*. 2000;31:1166-9. [PMID: 11073747]
19. Monto AS, Webster A, Keene O. Randomized, placebo-controlled studies of inhaled zanamivir in the treatment of influenza A and B: pooled efficacy analysis. *J Antimicrob Chemother*. 1999;44 Suppl B:23-9. [PMID: 10877459]
20. Nicholson KG, Aoki FY, Osterhaus AD, Trottier S, Carewicz O, Mercier CH, et al. Efficacy and safety of oseltamivir in treatment of acute influenza: a randomised controlled trial. *Neuraminidase Inhibitor Flu Treatment Investigator Group*. *Lancet*. 2000;355:1845-50. [PMID: 10866439]
21. Nicholson KG, Kent J, Hammersley V, Cancio E. Acute viral infections of upper respiratory tract in elderly people living in the community: comparative, prospective, population based study of disease burden. *BMJ*. 1997;315:1060-4. [PMID: 9366736]
22. Centers for Disease Control and Prevention. Reports & Surveillance Methods in the United States: Current U.S. Flu Report, 2002. Accessed at www.cdc.gov/ncidod/diseases/flu/weeklychoice.htm on 26 March 2002.
23. Barker WH, Mullooly JP. Impact of epidemic type A influenza in a defined adult population. *Am J Epidemiol*. 1980;112:798-811. [PMID: 7457471]
24. Nichol KL, Wuorenma J, von Sternberg T. Benefits of influenza vaccination for low-, intermediate-, and high-risk senior citizens. *Arch Intern Med*. 1998;158:1769-76. [PMID: 9738606]
25. Cox FM, Cobb MM, Chua WQ, McLaughlin TP, Okamoto LJ. Cost of treating influenza in emergency department and hospital settings. *Am J Manag Care*. 2000;6:205-14. [PMID: 10977420]
26. Libow LS, Neufeld RR, Olson E, Breuer B, Starer P. Sequential outbreak of influenza A and B in a nursing home: efficacy of vaccine and amantadine. *J Am Geriatr Soc*. 1996;44:1153-7. [PMID: 8855992]
27. Keyser LA, Karl M, Nafziger AN, Bertino JS Jr. Comparison of central nervous system adverse effects of amantadine and rimantadine used as sequential prophylaxis of influenza A in elderly nursing home patients. *Arch Intern Med*. 2000;160:1485-8. [PMID: 10826462]
28. Hayden FG, Treanor JJ, Fritz RS, Lobo M, Betts RF, Miller M, et al. Use of the oral neuraminidase inhibitor oseltamivir in experimental human influenza: randomized controlled trials for prevention and treatment. *JAMA*. 1999;282:1240-6. [PMID: 10517426]
29. Hayden FG, Treanor JJ, Betts RF, Lobo M, Esinhart JD, Hussey EK. Safety and efficacy of the neuraminidase inhibitor GG167 in experimental human influenza. *JAMA*. 1996;275:295-9. [PMID: 8544269]
30. Diggory P, Fernandez C, Humphrey A, Jones V, Murphy M. Comparison of elderly people's technique in using two dry powder inhalers to deliver zanamivir: randomised controlled trial. *BMJ*. 2001;322:577-9. [PMID: 11238150]
31. Govaert TM, Thijs CT, Masurel N, Sprenger MJ, Dinant GJ, Knottnerus JA. The efficacy of influenza vaccination in elderly individuals. A randomized double-blind placebo-controlled trial. *JAMA*. 1994;272:1661-5. [PMID: 7966893]
32. Demicheli V, Rivetti D, Deeks JJ, Jefferson TO. Vaccines for preventing influenza in healthy adults [Review]. *Cochrane Database Syst Rev*. 2001; CD001269. [PMID: 11687102]
33. Griffin AD, Perry AS, Fleming DM. Cost-effectiveness analysis of inhaled zanamivir in the treatment of influenza A and B in high-risk patients. *Pharmacoeconomics*. 2001;19:293-301. [PMID: 11303417]
34. 2001 Drug Topics Red Book. Montvale, NJ: Medical Economics; 2001.
35. Crane M. What you charge vs what you get. *Med Econ*. 2001;78:50-2, 55-7. [PMID: 11715372]
36. Rapid diagnostic tests for influenza. *Med Lett Drugs Ther*. 1999;41:121-2. [PMID: 10987012]
37. Dolin R, Reichman RC, Madore HP, Maynard R, Linton PN, Webber-Jones J. A controlled trial of amantadine and rimantadine in the prophylaxis of influenza A infection. *N Engl J Med*. 1982;307:580-4. [PMID: 7050702]
38. Relenza (zanamivir for inhalation) [Package insert]. Research Triangle Park, NC: Glaxo Wellcome; 2001.
39. Gold M, Siegel J, Russell L, Weinstein M, eds. *Cost-Effectiveness in Health and Medicine*. New York: Oxford Univ Pr; 1996.
40. U.S. Department of Labor, Bureau of Labor Statistics. Consumer Price Index—All Urban Consumers. Accessed at www.bls.gov/data/ on 6 May 2002.
41. Cost-effectiveness of intensive glycemic control, intensified hypertension control, and serum cholesterol level reduction for type 2 diabetes. *JAMA*. 2002;287:2542-51. [PMID: 12020335]
42. Kerlikowske K, Salzman P, Phillips KA, Cauley JA, Cummings SR. Continuing screening mammography in women aged 70 to 79 years: impact on life expectancy and cost-effectiveness. *JAMA*. 1999;282:2156-63. [PMID: 10591338]
43. Smith KJ, Roberts MS. Cost-effectiveness of newer treatment strategies for influenza. *Am J Med*. 2002;113:300-7. [PMID: 12361816]
44. Muennig PA, Khan K. Cost-effectiveness of vaccination versus treatment of influenza in healthy adolescents and adults. *Clin Infect Dis*. 2001;33:1879-85. [PMID: 11692300]
45. Stange KC, Little DW, Blatnik B. Adverse reactions to amantadine prophylaxis of influenza in a retirement home. *J Am Geriatr Soc*. 1991;39:700-5. [PMID: 2061537]
46. Gravenstein S, Davidson HE. Current strategies for management of influenza in the elderly population. *Clin Infect Dis*. 2002;35:729-37. [PMID: 12203171]

Current Author Addresses: Drs. Rothberg, Bellantonio, and Rose: Division of General Medicine and Geriatrics, Baystate Medical Center, 759 Chestnut Street, Springfield, MA 01199.

Author Contributions: Conception and design: M.B. Rothberg, D.N. Rose.

Analysis and interpretation of the data: M.B. Rothberg, D.N. Rose.

Drafting of the article: M.B. Rothberg, S. Bellantonio, D.N. Rose.

Critical revision of the article for important intellectual content: M.B. Rothberg, S. Bellantonio, D.N. Rose.

Final approval of the article: M.B. Rothberg, S. Bellantonio, D.N. Rose.

Statistical expertise: M.B. Rothberg, D.N. Rose.

Administrative, technical, or logistic support: D.N. Rose.

Collection and assembly of data: M.B. Rothberg.