Management of Influenza Symptoms in Healthy Adults
Cost-effectiveness of Rapid Testing and Antiviral Therapy
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OBJECTIVE: To determine the cost-effectiveness of rapid diagnostic testing and empiric antiviral therapy for healthy adults with symptoms of influenza.

DESIGN: Cost-effectiveness analysis using a decision model based on previously published data. Outcome measures included costs and quality-adjusted life expectancy.

SETTING: Physician’s office.

PATIENTS/PARTICIPANTS: Hypothetically healthy, working adults < 65 years of age presenting with cough and fever during the influenza season.

INTERVENTIONS: Rapid testing or clinical diagnosis followed by treatment with amantadine, rimantadine, oseltamir, or zanamivir compared with no antiviral therapy.

RESULTS: Base-case analysis: not giving antiviral therapy is the most expensive and least effective strategy, costing $471 per patient, mostly owing to time lost from work. Amantadine treatment increases life expectancy by 0.0014 quality-adjusted life years (QALYs) while saving $108 per patient relative to no antiviral therapy. Zanamivir is slightly more effective than amantadine, adding 0.0002 QALYs at an incremental cost of $31, or $133,000 per QALY saved. All other strategies, including testing strategies, are both less effective and more expensive.

SENSITIVITY ANALYSIS: The model is sensitive to the probability of influenza infection, proportion of influenza caused by type B, the relative efficacy of the various drugs, and the value of a workday. At a clinical probability of influenza infection > 20%, antiviral therapy is favored. As the proportion of influenza B increases, zanamivir is favored over amantadine. Testing is rarely indicated. Ignoring the costs of lost workdays, amantadine treatment costs $1,200/QALY saved.

CONCLUSIONS: Antiviral therapy with either amantadine or zanamivir is cost-effective for healthy, young patients with influenza-like illness during the influenza season, depending on the prevalence of influenza B.

KEY WORDS: influenza; cost-effectiveness; antiviral therapy; neuraminidase.

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fluenza virus infection typically occurs in winter epidemics, causing an estimated 20,000 deaths and more than 100,000 hospitalizations annually in the United States. Although vaccination efforts have been aimed largely at the elderly, the majority of cases and hospitalizations occur among persons younger than 65 years old. In addition, influenza accounts for $1 to $3 billion in direct medical costs and $10 to $15 billion in indirect costs, including lost productivity. Antiviral drugs for influenza infection have been available for more than 35 years. Amantadine and rimantadine, which are active only against influenza A infection, have been shown to decrease the duration of illness by approximately 1 day. A 5-day course of amantadine costs $2 and side effects are similar to placebo. Resistant strains emerge rapidly in treated patients, though the impact of this resistance is unknown.

In 1999, the neuraminidase inhibitors zanamivir and oseltamivir, both active against influenza A and B, were licensed in the United States. Well-conducted studies demonstrate that treatment with either drug reduces the duration of influenza symptoms in average-risk patients by 1 to 1.5 days. In addition, both drugs reduce the incidence of complications requiring antibiotics. Side effects and the emergence of drug resistance are uncommon. However, these newer agents are expensive, ranging from $48 to $80 for a 5-day course.

To be effective, antiviral therapy must be started within 48 hours of symptom onset. Unlike traditional viral cultures, which take several days to grow, newer rapid tests can diagnose influenza in the office in less than 30 min, facilitating immediate treatment. Four rapid tests are available, each with a different sensitivity and specificity. All tests can detect both influenza A and B, and one, Directigen AB (BD Diagnostic Systems, Sparks, Md), can differentiate between the two, allowing the physician to reserve treatment with a neuraminidase inhibitor for patients with influenza B infection. The tests cost between $15 and $25.

Is antiviral therapy cost-effective for healthy patients with influenza-like illness? If so, should treatment be based on clinical diagnosis or directed by rapid testing, and which test should be employed? Should standard therapy include the newer agents, or should they be reserved for patients with proven influenza B infection? In response to these questions, we constructed a decision-analytic model to determine the cost-effectiveness of empiric versus test-guided antiviral therapy compared to no antiviral therapy for patients presenting with symptoms of influenza.

METHODS

Decision Analytic Model

We constructed a simple decision tree using a standard computer program (Decision Maker 7.07, Pratt Medical
Group, Boston, Mass) to compare the following strategies: (1) no antiviral therapy; (2) empirical treatment with either amantadine, rimantadine, oseltamivir, or zanamivir; (3) rapid testing with one of the nondiscriminating tests followed by treatment with one of the four antiviral drugs; and (4) rapid testing with Directigen AB, followed by treatment with amantadine or rimantadine for influenza A infection and zanamivir or oseltamivir for influenza B infection. A graphical representation of the model is shown in Figure 1.

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

For the reference case, we considered unvaccinated, healthy, working adults between 20 and 50 years of age presenting with influenza-like illness during the influenza season. The model considers the prevalence of influenza, sensitivity and specificity of the tests, and the following adverse events: antiviral side effects, influenza complications requiring antibiotics, emergency room visits, hospitalizations, and deaths. Influenza infection is divided into types A and B, which we assumed to be of equal severity. We assumed that only neuraminidase inhibitors would be effective in treating influenza B. Outcomes were expressed in dollars per quality-adjusted life year (QALY) saved.

**Data and Assumptions**

Baseline estimates and range for sensitivity analyses are provided in Table 1.

**Influenza Prevalence and Complications.** Influenza occurs in winter epidemics. For our base case, we analyzed patients presenting during the peak flu season (usually December through March in the northern hemisphere) in a region with documented influenza cases. In such a setting, patients with influenza-like illness, defined as abrupt onset of fever > 37.8°C plus 2 of 4 symptoms (cough, myalgia, sore throat, and headache) have a 70% to 87% chance of having influenza. If influenza has not been documented in the area, the positive predictive value of these symptoms drops to between 44% and 60%. During the peri-influenza season (usually October, November, April, and May), patients with the same symptoms have less than a 20% chance of having influenza.

The proportion of influenza infections caused by influenza B changes every year. In 2002, approximately 11% of influenza specimens were type B. In past years, the proportion has been as high as 63% in some regions. We used 2001–02 as our base season, but tested a broad range of proportions in the sensitivity analysis.

Complications requiring antibiotics were based on the experience of subjects in the placebo arms of treatment trials. We used published estimates for hospitalization rates of healthy young women and healthy patients under 65 years of age. These correlate closely with the hospitalization rate among placebo recipients in the zanamivir treatment trials. The death rate was expressed as a function of the hospitalization rate, as described by Simonsen et al.