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# Treat or test first? Decision analysis of empirical antiviral treatment of influenza virus infection versus treatment based on rapid test results

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## Abstract

**Background:** neuraminidase (NA) inhibitors have recently become available for treatment of influenza. Rapid antigen detection assays at ‘point-of-care’ may improve the accuracy of clinical diagnosis, but the value of these techniques in assisting with the appropriate use of antivirals remains controversial. **Objective:** to compare the diagnostic utilities of two management strategies for influenza, empirical antiviral therapy versus therapy based on a positive rapid test result in pre-epidemic and epidemic periods. **Study design:** a threshold decision analytic model was designed to compare these competing strategies and sensitivity analysis performed to examine the impact of diagnostic variables on the expected utility of the decision with a range of prior probabilities of infection between 1 and 50%. **Results:** on the basis of the calculated sensitivity (77%) and specificity (95%) of a point-of-care test for influenza, pre-treatment testing was preferred and cost-effective in non-epidemic stage of the influenza cycle. The alternative strategy of empirical treatment produces a higher utility value during epidemics, but may result in overuse of antivirals for low-risk populations. The two strategies had equivalent efficacy when the probability of influenza was 42%. **Conclusions:** Patients with flu-like illness, who present outside the influenza outbreak and are considered to be at low risk for influenza-related complications, should be tested to confirm the diagnosis before starting antiviral treatment with a NA inhibitor. The most important variables in the model were the accuracy of the clinical diagnosis and the pre-test probability of influenza. A threshold probability of influenza of 42% would dictate changing from the rapid testing strategy to a ‘treat regardless’ strategy. © 2002 Elsevier Science B.V. All rights reserved.

**Keywords:** Decision analysis; Influenza; Laboratory diagnosis; Treatment

## 1. Introduction

New neuraminidase (NA) inhibitors with broad-spectrum activity against all nine influenza A subtypes and influenza B have recently become

*Abbreviations:* NA, neuraminidase.

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available for treatment and prophylaxis of influenza. Inhaled zanamivir (Relenza<sup>®</sup>) is now licensed in Northern America, Europe and Australia and oral oseltamivir (Tamiflu<sup>®</sup>) has been approved in Canada, Switzerland, and USA. They can significantly reduce the severity and duration of symptoms, time taken to return to normal activities and use of antibiotics and relief medications in both the general population and in patients at high risk for complications (Hayden et al., 1997, 1999; Monto et al., 1999a; Gubareva et al., 2000). However, for therapy to be effective it needs to be commenced within 36–48 h of onset of illness.

Influenza virus infections typically occur in outbreaks lasting 8–12 weeks during winter, and are uncommon outside these periods. Diagnosis of influenza on clinical grounds alone is both insensitive and non-specific in non-epidemic situations (Carrat et al., 1997; Nicholson et al., 1998). Although cell culture remains the gold standard for the laboratory diagnosis and surveillance of influenza, it has limited clinical utility because results are obtained too late for effective intervention. Rapid diagnostic assays for influenza have demonstrated high specificity, but poor sensitivity compared with cell culture (Johnston and Seigel, 1991; Doing et al., 1998) and their role in the diagnosis of influenza and initiation of treatment remains unclear. It is expected that by combining the clinical diagnosis of influenza with office-based rapid testing, candidates for antiviral treatment will be better selected.

The purpose of this study was to compare two strategies for management of clinical influenza using new data on the performance of commercial rapid tests and efficacy of influenza treatment. Decision analysis is a popular tool to structure a clinical problem and to identify the main determinants of diagnostic and therapeutic choice (Lilford et al., 1998). It uses Bayesian probabilities together with values assigned to different outcomes to determine the best course of action. We chose a threshold model of decision analysis to compare the value of empirical treatment with the treatment of clinical influenza based on rapid test results.

## 2. Materials and methods

### 2.1. Comparative strategies

In the model, we considered adult patients with influenza-like illness who did not require hospital admission. The alternative management strategies are (a) empirical treatment with a NA inhibitor, or (b) treatment with NA inhibitor of patients with suspected influenza confirmed by rapid testing. There are now the most common options in community practice during annual influenza epidemic activity. We created a decision analysis tree (Fig. 1) that includes two branches of competing strategies for patients with clinical diagnosis of influenza, and one branch for patients in whom the diagnosis was excluded. Patients with suspected influenza who are tested by rapid antigen assays would be either ‘positive’ or ‘negative’. Antiviral treatment would be offered only to patients in the branch where testing is performed, in whom the test is positive.

According to the threshold model, the choice of a particular clinical strategy is dictated by the probability of disease’s exceeding relevant threshold probability (Lilford et al., 1998). A utility (i.e. numeric value) represents our preferences for one outcome over others. They are quantified on a scale from 0 to 1 to allow comparison between alternative outcomes. It is a basic concept of decision analysis that the option selected should be the one with the highest expected utility because this choice should, on the average, produce an optimal outcome.

### 2.2. Probability values

The probabilities used in the decision analysis were based on expert opinion and those from the literature (Table 1). Probability rates in our analysis (0.01, 0.1, 0.3 and 0.5) have been chosen to correspond respectively to pre-epidemic influenza community attack rates (less than 10%), to rates of disease achieved during community epidemics (10–50%) and in closed environments such as families, nursing homes and military camps (range between 30 and 87%, average 45%) (Curran and Hampson, 1997; Webster, 1998). Disease due to

influenza virus infection cannot be readily distinguished on clinical grounds from other acute respiratory virus infections. The accuracy of clinical assessment varies between 30 and 80%, and even during outbreaks only about 50% of influenza-like illnesses are virologically confirmed (Nicholson et al., 1998). Therefore, we opted to rely on optimistic point-estimates for the accuracy of clinical diagnosis of influenza published for unselected patients (Table 1) (Monto and Sullivan, 1993; Nicholson et al., 1998; Webster, 1998).

Office-based assays for influenza A and B virus detection in respiratory specimens have recently become available. These assays provide a result within 10–15 min. of collecting the sample. We assumed equal performance for the commercially available kits and used performance characteristics of the Quidel Rapid Influenza test (Quidel Corporation, 10165 McKeller Court, San Diego, CA 92121) as base-line values. The sensitivity and specificity of this kit were 77 and 95%,

respectively, when prospectively compared with viral culture in our laboratory during the 1999 influenza seasons in New South Wales, Australia (unpublished data).

### 2.3. Decision analysis

Two competing clinical strategies were defined, and baseline values of the probabilities of each test result, diagnosis and outcome were estimated and incorporated into the decision tree (Fig. 1). After the path probabilities of each branch of the tree were calculated we gave arbitrary numerical assignments to the utility value (a relative desirability of a given outcome) to each of four possible outcomes (Pauker and Kassirer, 1975). On an average, 5 and 10% of patients on zanamivir experience significant adverse reactions and minor side-effects, respectively (Freund et al., 1999; Gubareva et al., 2000; Williamson and Pegram, 2000). Thus, we calculated utilities for ‘treated

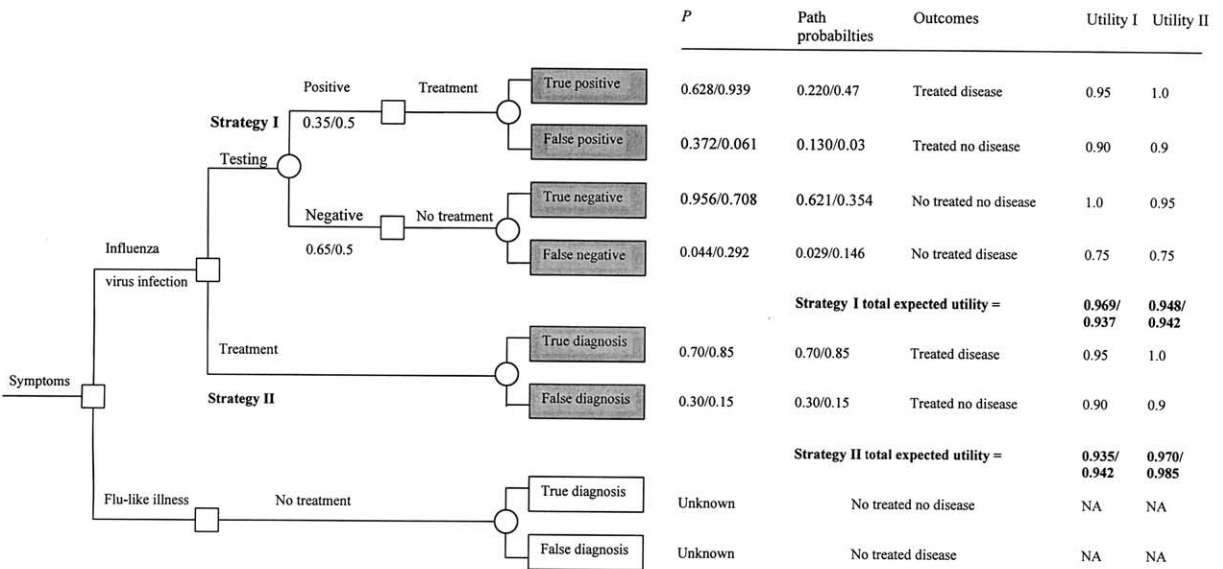


Fig. 1. Decision tree for ‘test first and treat after’ (Strategy I) and ‘treat regardless’ (Strategy II) approaches to the management of patients with flu-like symptoms in out-patient setting. The squares in the decision tree indicate a decision node. If one branch continues from a decision node, only one decision is possible. The chance nodes represented by circles are used, if subsequent outcomes occur by chance. Probabilities of outcomes (P) for selected prevalence of influenza (10/50%) are shown. Utility I, utility value for uncomplicated influenza case; Utility II, utility value for patients with risk factors for complications. Expected utility is the sum of each outcome path probabilities multiplied by respective utility. NA, not applicable.

Table 1

Baseline values and ranges (%) of variables and test characteristics used to construct the decision tree for comparing two strategies for managing clinical influenza

Variable	Baseline value	Range	Data sources or reference
Pre-test probability of influenza	10	5–87	Nicholson et al., 1998; Monto et al., 1999b
Accuracy of clinical diagnosis of influenza	60	30–80	Carrat et al., 1997; Nicholson et al., 1998
Probability of patient being positive for rapid test	35	5–55	Expert opinion and our own data
Rapid testing sensitivity	77	64–88	Doing et al., 1998; Kaiser et al., 1999; Monto and Sullivan, 1993; Covalciuc et al., 1999
Rapid testing specificity	95	76–97	Doing et al., 1998; Kaiser et al., 1999; Monto and Sullivan, 1993; Covalciuc et al., 1999

disease' outcome and 'treated no disease' outcome as 0.95 and 0.90. Utility for the 'no treated disease' outcome was assumed to be 0.75, because the mortality rate of untreated influenza in high-risk group is up to 25% (Nicholson et al., 1998). We opted for base-line analysis to put the maximum value (1.0) on the prevention of unnecessary treatment of non-influenza viral respiratory infections ('no treated no disease') that dominate in general practice. However, for high-risk patients (elderly patients with chronic medical conditions such as heart or lung disease, renal failure, immune disorder, pregnant women and heavy smokers) a separate scale of utilities, with maximum value for the treatment of infection, was used for decision analysis. For the sake of simplicity, the flu-like illness branch of the tree was not considered in the comparison due to the equal influence on each strategy under evaluation and uncertainties of this branch's outcomes.

Sensitivity analysis was done to test the robustness of the conclusions drawn. The influence of variable prevalence of disease, probability of a positive rapid test, its specificity and sensitivity and utility of outcome on the resulting value of the strategy, have been tested in the sensitivity analysis to see whether the optimal strategy changed. Each individual estimate (one-way sensitivity analysis) or two probability estimates simultaneously (two-way sensitivity analysis) were varied according to the range of values determined from the literature and expert opinion (Table 1).

### 3. Results

#### 3.1. Probability of accurate diagnosis of infection

The decision tree indicates that, in the non-epidemic scenario (probability of infection  $\leq 10\%$ ), up to 30% of patients who receive empirical treatment would have a non-influenza respiratory infection. The use of the 'test and treat' approach would reduce over-treatment to 13%. However, during an outbreak when the community influenza attack rate is between 10 and 30%, a proportion of patients with influenza (4–15%) may miss specific treatment due to false-negative rapid test result. As expected, increase of prior probability of infection during an outbreak results in better accuracy of clinical diagnosis. Inappropriate empirical treatment in this scenario becomes less likely due to a smaller proportion of incorrect diagnoses (15 vs. 17.6%).

#### 3.2. Decision thresholds

Comparison of expected utilities of competing strategies for different prior probabilities of influenza (Fig. 2) provided a decision threshold for change in the management approach. The prevalence of influenza of 42% would dictate changing from rapid testing strategy to 'treat regardless' strategy. However, when utility scale for high-risk patients was used (with maximum utility of treatment of disease rather than no treatment no disease) the empirical treatment strategy became preferable for any given probability of influenza.

### 3.3. Sensitivity analyses

One-way sensitivity analysis with expected utility as the outcome, while each probability, assay performance and utility was allowed to vary individually, showed that rapid testing is helpful when the prior probability of disease is below 40%, which corresponds to the non-epidemic and early epidemic stages of the influenza cycle. Varying the point-of-care test sensitivity between 50 and 97%, and the rate of rapid test positivity from 0.2 to 0.6 produced no change in the expected utility values of the strategy. The model was most sensitive to variations in the accuracy of clinical diagnosis that depends largely on prior probability of influenza and the utility placed on particular outcomes. Thus, two-way sensitivity analysis provided estimates for physicians whose patients experience different influenza attack rates. With an accuracy of clinical assessment for influenza of less than 50%, the empirical treatment strategy would be less preferable even in a high prevalence scenario. Increasing the sensitivity of rapid testing from 77 to 97% would make the ‘test-and-treat’ strategy the more beneficial intervention across the range of different probabilities of disease.

### 4. Discussion

The major finding of this study is that patients who have flu-like illness, but are considered to be at low risk for influenza-related complications, should be tested to confirm the diagnosis of influenza virus infection before starting antiviral treatment with a NA inhibitor. This choice is associated with both a higher expected utility and a lower cost in most circumstances. The higher cost of the empirical treatment strategy, however, becomes preferable at the peak time of influenza activity when the community attack rate exceeds 42%. For high-risk patients, particularly individuals not covered or inadequately protected by vaccination, promptly administered empirical treatment is likely to be a safer, but more costly alternative regardless of the baseline prevalence of disease.

The choice between the two strategies discussed involves a trade-off between the higher specificity of test result-based strategy and the reduced risk of complications of therapy. Confidence intervals or statistical significance are not determined in decision analysis. Given that a majority of res-

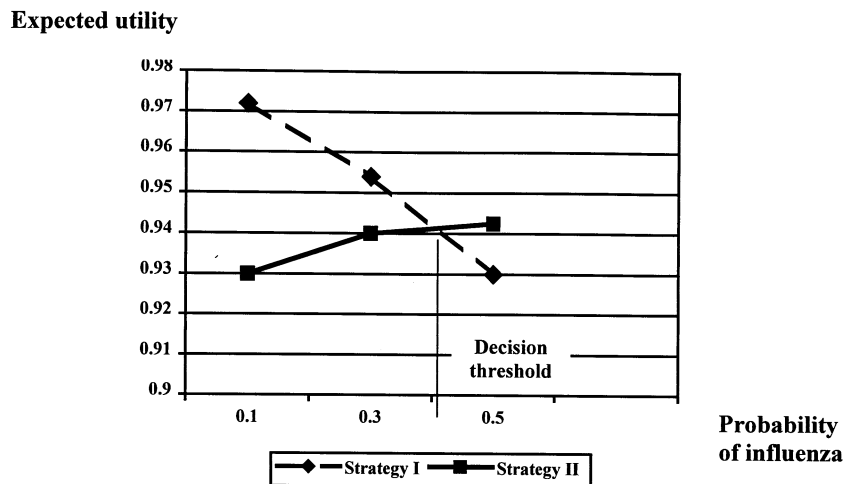


Fig. 2. One-way sensitivity analysis of the decision tree to determine the effect of the prevalence of influenza on the expected utility (the sum of outcome probability multiplied by respective utility) of each strategy. Where the lines of the strategies intersect, this intersection defines a threshold point. If the prevalence of influenza is below the threshold, the ‘test-first-then-treat’ strategy is optimal; if this prevalence is above the threshold, then the alternative empirical treatment is optimal. Strategies are as in Fig. 1.

piratory infections outside the influenza epidemic are caused by other pathogens, 25–30% unnecessary use of expensive treatment due to false positive clinical diagnoses are hardly justifiable. Importantly, the evidence to support the use of NA inhibitors in patients with risk-factors for influenza-related complications remains limited due to small numbers of these patients included in trials (Gubareva et al., 2000). Furthermore, recent European experience showed that the majority of the patients receiving influenza antivirals are young adults who do not have risk factors for influenza-related complications but are keen to return to work sooner (Dr S. Andersen, Glaxo Wellcome, personal communication, February 2000). Under the assumed baseline values, the probability of receiving treatment unnecessarily could be reduced from 0.25 to 0.13 by using a point-of-care assay. Although it adds additional cost and time to a consultation, the cost of antiviral overuse and potential side-effects exceed the cost of testing. In addition, although clinical resistance to NA inhibitors has not yet emerged as a clinical problem, monitoring of patients using these drugs is warranted.

Comparative studies of the rapid tests and their reproducibility are also lacking. Although the data used in this evaluation are for the Quidel A/B assay, the findings would apply to other available tests as well (e.g., FLU OIA, Directigen Flu A, Flu A/B test etc.). Tests based on antigen detection have a sensitivity of approximately 64 to 80%, which is comparable with clinical evaluation by an experienced clinician. Nasopharyngeal washes are the most sensitive sample types, if performed on day 2 or 3 after the onset of infection (Kaiser et al., 1999). According to our model, a rapid test result-based treatment strategy would be preferable to empirical treatment for high-risk patients or when there is a high probability of influenza, only if the sensitivity exceeded 97%. This level of sensitivity is unlikely to be achieved by rapid antigen detection systems, but is a reasonable target for a nucleic acid amplification system. Thus, real-time polymerase chain reaction-based assay may open a new era of clinical management of influenza.

The key variable of both management strategies remains the accuracy of clinical assessment. Unfortunately, influenza case definitions vary significantly (Curran and Hampson, 1997). The use of stringent case definition during extensive outbreaks allows identification of 70–80% of influenza-infected patients using clinical diagnosis alone (The MIST Study Group, 1998), supporting the notion that empiric therapy may be a cost-effective option at this time without incurring the additional expense of treating large numbers of patients who do not have influenza. Our model shows the critical importance of relative utility of expected outcomes in influenza management decision-making. The question whether studies focused on intermediate outcomes (e.g., time to return to normal activities, use of relief medications) provide enough evidence to justify preference of empirical treatment over watchful waiting remains unanswered. The prevalence of disease in the community was also important in this model. This finding emphasizes the value of both timely influenza surveillance programs and conventional laboratory confirmation of clinical diagnosis for monitoring of outbreaks and notifying medical practitioners about the prevalence of influenza in the community.

There are several limitations in this study. First, these analyses are based on limited data on accuracy of clinical and laboratory diagnosis of infection and expert opinions rather than best quality evidence. However, the aim of decision analytic techniques is to improve the quality of decisions made with uncertain and incomplete information and identify deficiencies in data to be addressed in future studies. We have not incorporated the impact of antivirals on the incidence of secondary infection (Hayden et al., 1997), nor the patient's preferences in the utility assessment. Positive predictive value of the rapid testing, when utilized in the 'pre-outbreak' time, may be significantly lower than we assumed. Lastly, we have limited our model to uncomplicated influenza in adults and have not included some potentially important variables, such as physician attitudes, impact of influenza vaccination rates or type and virulence of particular circulating influenza virus (Curran and Hampson, 1997).

In summary, this model allows us to examine interactions of combinations of variables according to the available evidence and the perceived values of clinicians and patients. The analysis shows that treatment of influenza on grounds of clinical diagnosis is a favored management strategy compared with treatment based on rapid test results during influenza epidemic seasons, however, the state of the evidence does not permit more firm conclusions. There is a need to maintain high quality laboratory surveillance for rational health care resource utilization.

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